```
                                        Nhe I          Linker
1    GAT CCA GCA GCT GGG CTC GAG GTG CTA GCG GGA GGG GGT GGA TGT GGG
      D   P   A   A   G   L   E   V   L   A   G   G   G   G   C   G

                 Xa
      Factor Xa  ↓ Hind III          hu IgG1
49   ATC GAA GGT CGC AAG CTT ACT CAC ACA TGC CCA CCG TGC CCA GCA CCT
      I   E   G   R   K   L   T   H   T   C   P   P   C   P   A   P

97   GAA GCC GAG GGG GCA CCG TCA GTC TTC CTC TTC CCC CCA AAA CCC AAG
      E   A   E   G   A   P   S   V   F   L   F   P   P   K   P   K

145  GAC ACC CTC ATG ATC TCC CGG ACC CCT GAG GTC ACA TGC GTG GTG GTG
      D   T   L   M   I   S   R   T   P   E   V   T   C   V   V   V

193  GAC GTG AGC CAC GAA GAC CCT GAG GTC AAG TTC AAC TGG TAC GTG GAC
      D   V   S   H   E   D   P   E   V   K   F   N   W   Y   V   D

241  GGC GTG GAG GTG CAT AAT GCC AAG ACA AAG CCG CGG GAG GAG CAG TAC
      G   V   E   V   H   N   A   K   T   K   P   R   E   E   Q   Y

289  AAC AGC ACG TAC CGT GTG GTC AGC GTC CTC ACC GTC CTG CAC CAG GAC
      N   S   T   Y   R   V   V   S   V   L   T   V   L   H   Q   D

337  TGG CTG AAT GGC AAG GAG TAC AAG TGC AAG GTC TCC AAC AAA GCC CTC
      W   L   N   G   K   E   Y   K   C   K   V   S   N   K   A   L

385  CCA GCC TCC ATC GAG AAA ACC ATC TCC AAA GCC AAA GGG CAG CCC CGA
      P   A   S   I   E   K   T   I   S   K   A   K   G   Q   P   R

433  GAA CCA CAG GTG TAC ACC CTG CCC CCA TCC CGG GAT GAG CTG ACC AAG
      E   P   Q   V   Y   T   L   P   P   S   R   D   E   L   T   K

481  AAC CAG GTC AGC CTG ACC TGC CTG GTC AAA GGC TTC TAT CCC AGC GAC
      N   Q   V   S   L   T   C   L   V   K   G   F   Y   P   S   D

529  ATC GCC GTG GAG TGG GAG AGC AAT GGG CAG CCG GAG AAC AAC TAC AAG
      I   A   V   E   W   E   S   N   G   Q   P   E   N   N   Y   K

577  ACC ACG CCT CCC GTG TTG GAC TCC GAC GGC TCC TTC TTC CTC TAC AGC
      T   T   P   P   V   L   D   S   D   G   S   F   F   L   Y   S

625  AAG CTC ACC GTG GAC AAG AGC AGG TGG CAG CAG GGG AAC GTC TTC TCA
      K   L   T   V   D   K   S   R   W   Q   Q   G   N   V   F   S

673  TGC TCC GTG ATG CAT GAG GCT CTG CAC AAC CAC TAC ACG CAG AAG AGC
      C   S   V   M   H   E   A   L   H   N   H   Y   T   Q   K   S

721  CTC TCC CTG TCT CCG GGT AAA TGA C
      L   S   L   S   P   G   K   -
```

FIG. 1A

```
                                               Nhe I              Linker
1   GAT CCA GCA GCT GGG CTC GAG GTG CTA GCG GGA GGG GGT GGA TGT GGG
     D   P   A   A   G   L   E   V   L   A   G   G   G   G   C   G

                       EK
         Enterokinase  ↓ Hind III              hu IgG1
49  GAC GAT GAC GAC AAG CTT ACT CAC ACA TGC CCA CCG TGC CCA GCA CCT
     D   D   D   D   K   L   T   H   T   C   P   P   C   P   A   P
```

FIG. 1B

```
1   ATG GAG ACA GAC ACA CTC CTG CTA TGG GTA CTG CTG CTC TGG GTT CCA
     M   E   T   D   T   L   L   L   W   V   L   L   L   W   V   P

                           Hind III                         Nhe I
49  GGT TCC ACT GGT GAC GCG GAT CCA GCA GCT GGG CTC GAG GTG CTA GCG
     G   S   T   G   D   A   D   P   A   A   G   L   E   V   L   A

                                                   EK
              Linker              Enterokinase     ↓ Hind III      hu IgG1
97  GGA GGG GGT GGA TGT GGG GAC GAT GAC GAC AAG CTT ACT CAC ACA TGC
     G   G   G   G   C   G   D   D   D   D   K   L   T   H   T
```

FIG. 1C

```
1   GGA TCC GGG ATG AAG AAC CTT TCA TTT CCC CTC CTT TTC CTT TTC TTC CTT
                M   K   N   L   S   F   P   L   L   F   L   F   F   L

52  GTC CCT GAA CTG CTG GGC TCC AGC ATG CCA CTG TGT CCC ATC GAT GAA GCC
    V   P   E   L   L   G   S   S   M   P   L   C   P   I   D   E   A

103 ATC GAC AAG AAG ATC AAA CAA GAC TTC AAC TCC CTG TTT CCA AAT GCA ATA
    I   D   K   K   I   K   Q   D   F   N   S   L   F   P   N   A   I

154 AAG AAC ATT GGC TTA AAT TGC TGG ACA GTC TCC TCC AGA GGG AAG TTG GCC
    K   N   I   G   L   N   C   W   T   V   S   S   R   G   K   L   A

205 TCC TGC CCA GAA GGC ACA GCA GTC TTG AGC TGC TCC TGT GGC TCT GCC TGT
    S   C   P   E   G   T   A   V   L   S   C   S   C   G   S   A   C

256 GGC TCG TGG GAC ATT CGT GAA GAA AAA GTG TGT CAC TGC CAG TGT GCA AGG
    G   S   W   D   I   R   E   E   K   V   C   H   C   Q   C   A   R

307 ATA GAC TGG ACA GCA GCC CGC TGC TGT AAG CTG CAG GTC GCT TCC TCT CTA
    I   D   W   T   A   A   R   C   C   K   L   Q   V   A   S   S   L

358 GCG GGA GGG GGT GGA TGT GGG ATC GAA GGT CGC AAG CTT ACT
    A   G   G   G   G   C   G   I   E   G   R   K   L   T
```

FIG. 2A

```
1   GGA TCC GGG ATG AAG AAC CTT TCA TTT CCC CTC CTT TTC CTT TTC TTC CTT
                M   K   N   L   S   F   P   L   L   F   L   F   F   L

52  GTC CCT GAA CTG CTG GGC TCC AGC ATG CCA CTG TGT CCC ATC GAT GAA GCC
    V   P   E   L   L   G   S   S   M   P   L   C   P   I   D   E   A

103 ATC GAC AAG AAG ATC AAA CAA GAC TTC AAC TCC CTG TTT CCA AAT GCA ATA
    I   D   K   K   I   K   Q   D   F   N   S   L   F   P   N   A   I

154 AAG AAC ATT GGC TTA AAT TGC TGG ACA GTC TCC TCC AGA GGG AAG TTG GCC
    K   N   I   G   L   N   C   W   T   V   S   S   R   G   K   L   A

205 TCC TGC CCA GAA GGC ACA GCA GTC TTG AGC TGC TCC TGT GGC TCT GCC TGT
    S   C   P   E   G   T   A   V   L   S   C   S   C   G   S   A   C

256 GGC TCG TGG GAC ATT CGT GAA GAA AAA GTG TGT CAC TGC CAG TGT GCA AGG
    G   S   W   D   I   R   E   E   K   V   C   H   C   Q   C   A   R

307 ATA GAC TGG ACA GCA GCC CGC TGC TGT AAG CTG CAG GTC GCT TCC TCT CTA
    I   D   W   T   A   A   R   C   C   K   L   Q   V   A   S   S   L

358 GCG GGA GGG GGT GGA TGT GGG GAC GAT GAC GAC AAG CTT ACT
    A   G   G   G   G   C   G   D   D   D   D   K   L   T
```

FIG. 2B

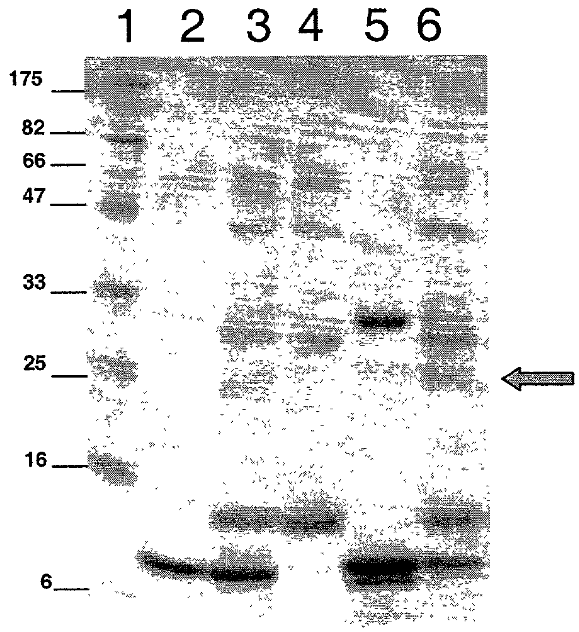


FIG. 2C

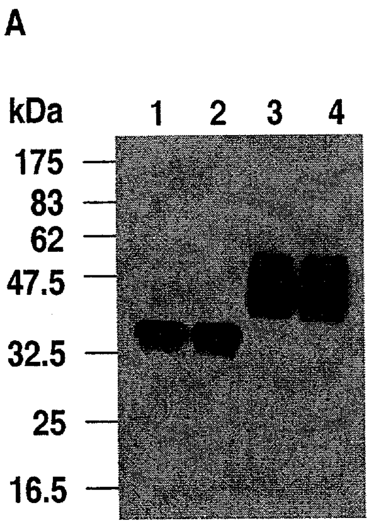

A
kDa
1 2 3 4
175
83
62
47.5
32.5
25
16.5

FIG. 3A

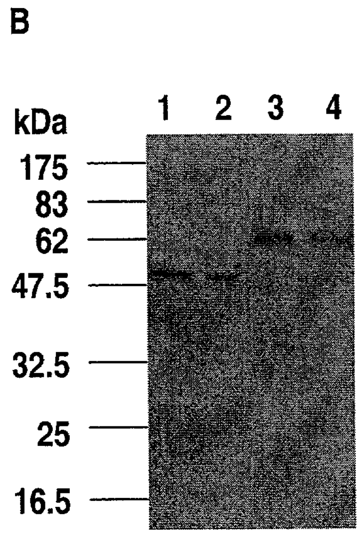
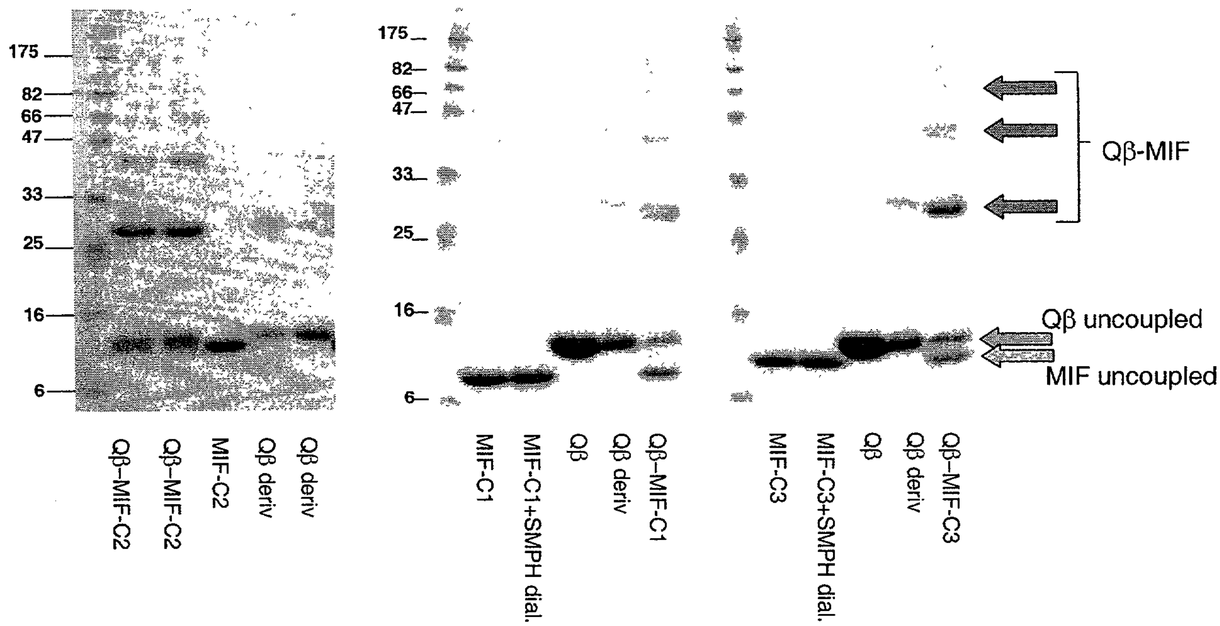

B
kDa
1 2 3 4
175
83
62
47.5
32.5
25
16.5

FIG. 3B



175
82
66
47
33
25
16
6
Qβ–MIF-C2
Qβ–MIF-C2
MIF-C2
Qβ deriv
Qβ deriv
175
82
66
47
33
25
16
6
MIF-C1
MIF-C1+SMPH dial.
Qβ
Qβ deriv
Qβ–MIF-C1
MIF-C3
MIF-C3+SMPH dial.
Qβ
Qβ deriv
Qβ–MIF-C3
Qβ-MIF
Qβ uncoupled
MIF uncoupled

FIG. 4A

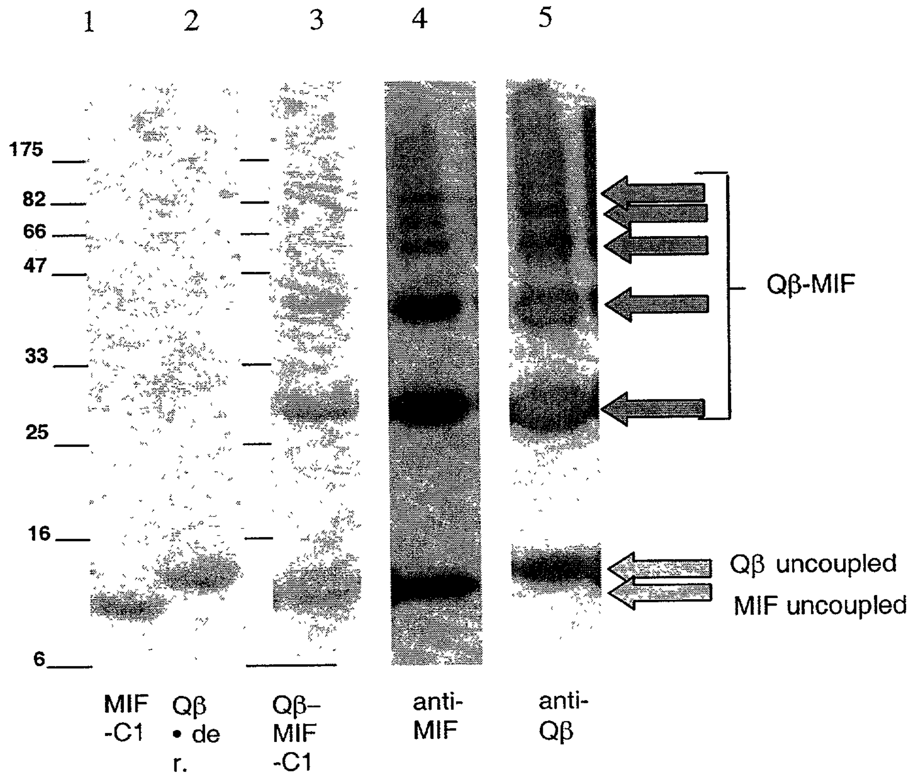

1
2
3
4
5
175
82
66
47
33
25
16
6
Qβ-MIF
Qβ uncoupled
MIF uncoupled
MIF -C1
Qβ • de r.
Qβ– MIF -C1
anti- MIF
anti- Qβ

FIG. 4B

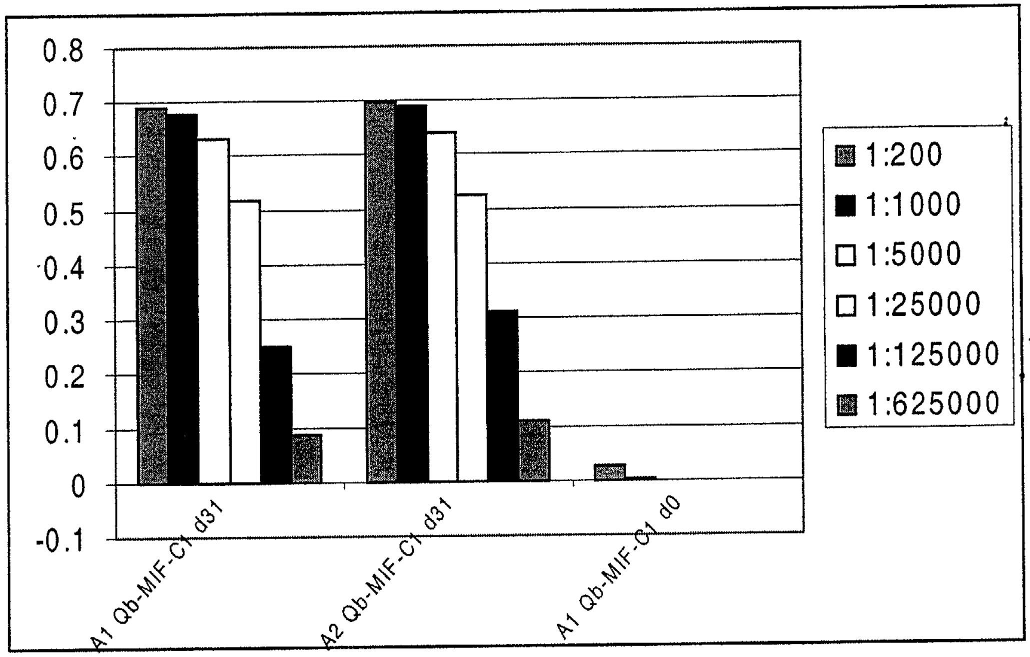

0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
-0.1
A1 Qb-MIF-C1 d31
A2 Qb-MIF-C1 d31
A1 Qb-MIF-C1 d0
1:200
1:1000
1:5000
1:25000
1:125000
1:625000

FIG. 4C

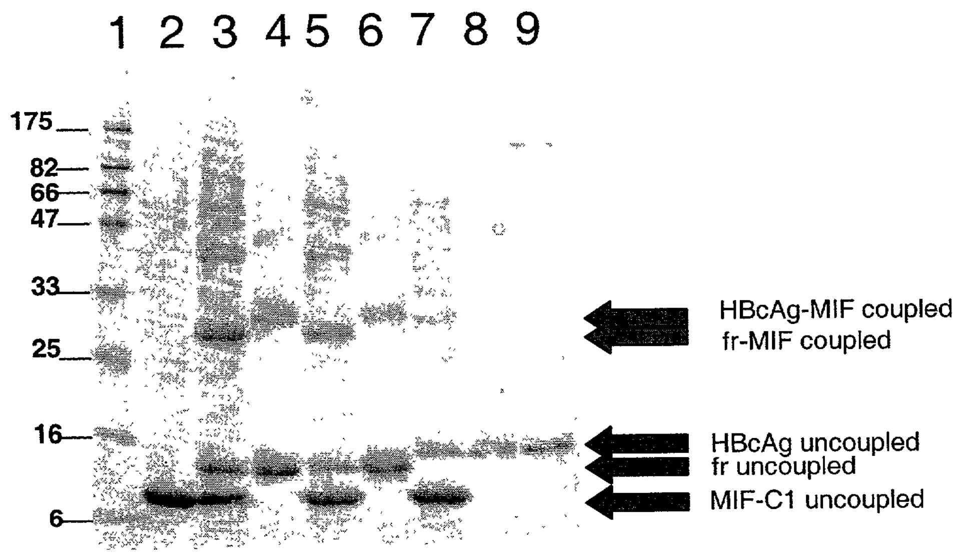

1 2 3 4 5 6 7 8 9
175
82
66
47
33
25
16
6
HBcAg-MIF coupled
fr-MIF coupled
HBcAg uncoupled
fr uncoupled
MIF-C1 uncoupled

FIG. 5

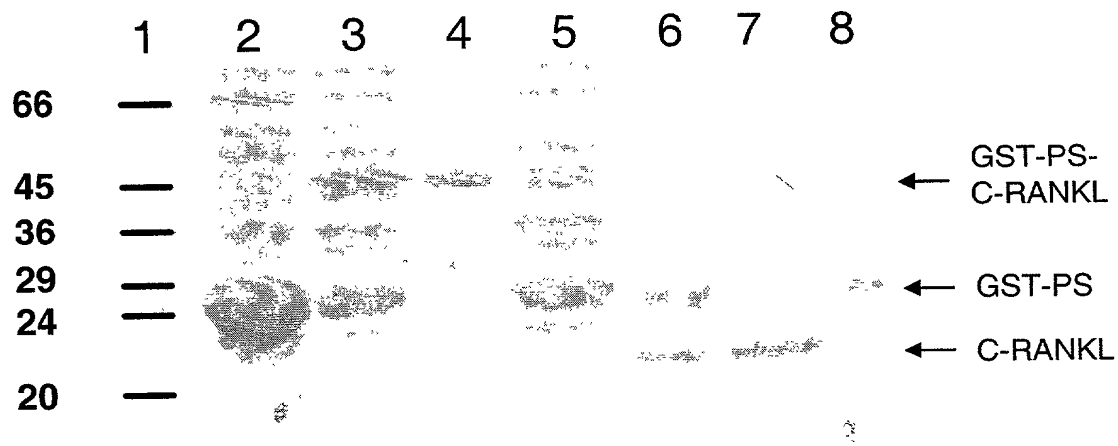


FIG. 6

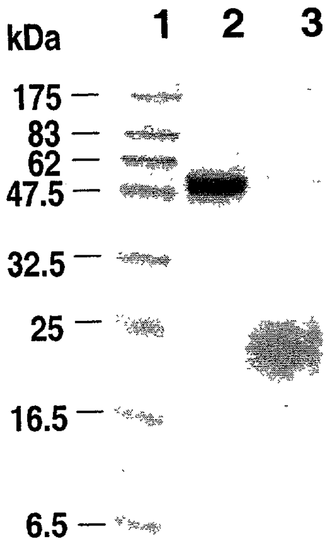


Fig 7

FIG. 8A

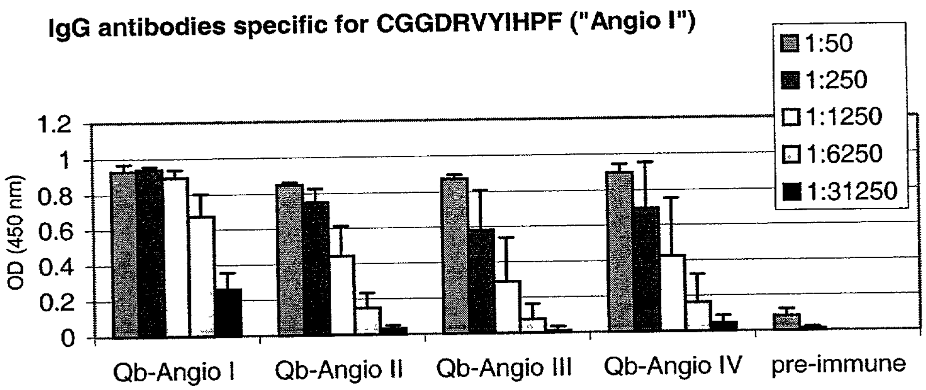


FIG. 8B

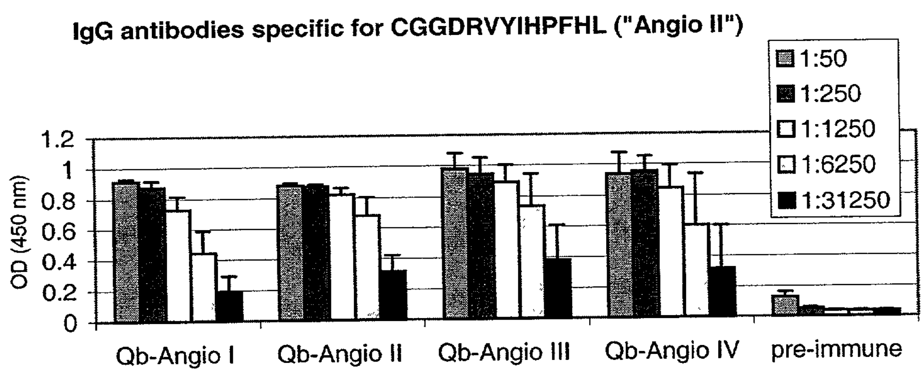


FIG. 8C

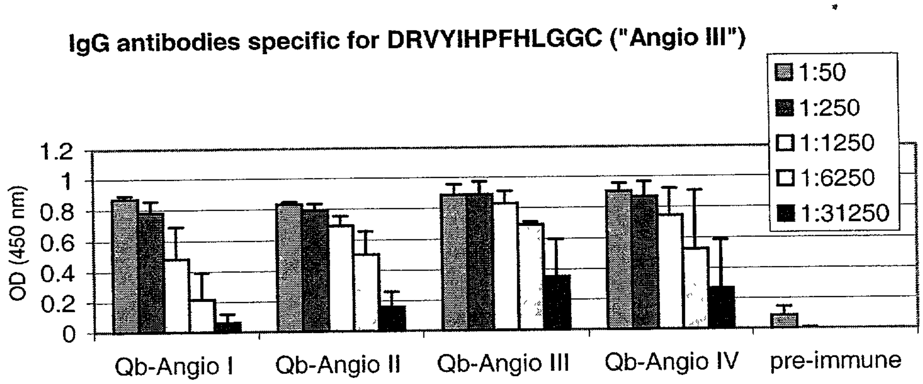


FIG. 8D

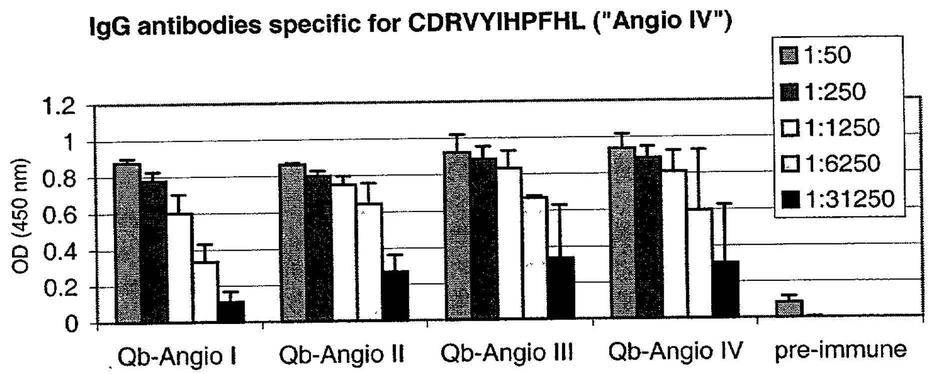

IgG antibodies specific for CDRVYIHPFHL ("Angio IV")
1:50
1:250
1:1250
1:6250
1:31250
OD (450 nm)
1.2
1
0.8
0.6
0.4
0.2
0
Qb-Angio I
Qb-Angio II
Qb-Angio III
Qb-Angio IV
pre-immune

FIG. 9A

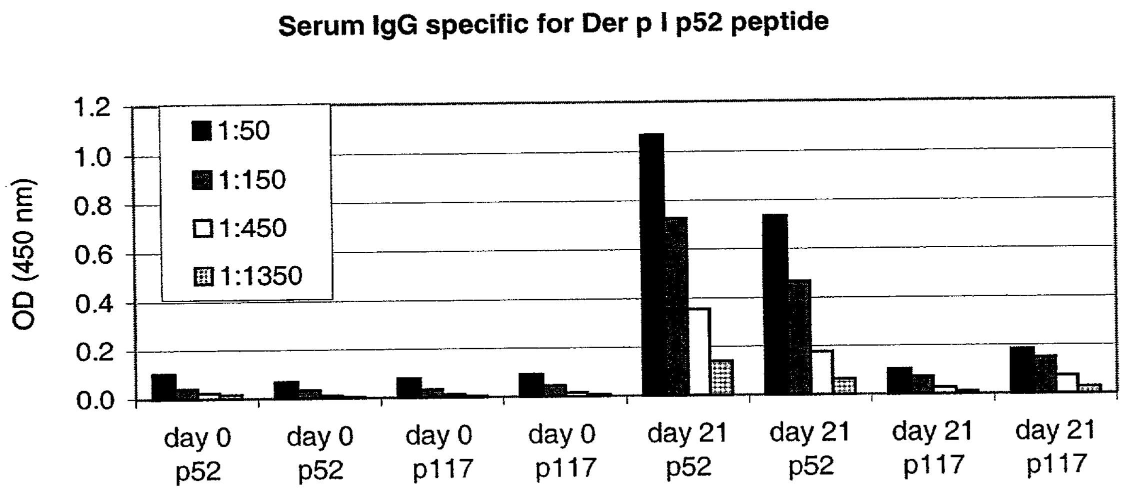

Serum IgG specific for Der p I p52 peptide
1.2
1.0
0.8
0.6
0.4
0.2
0.0
OD (450 nm)
1:50
1:150
1:450
1:1350
day 0 p52
day 0 p52
day 0 p117
day 0 p117
day 21 p52
day 21 p52
day 21 p117
day 21 p117

FIG. 9B

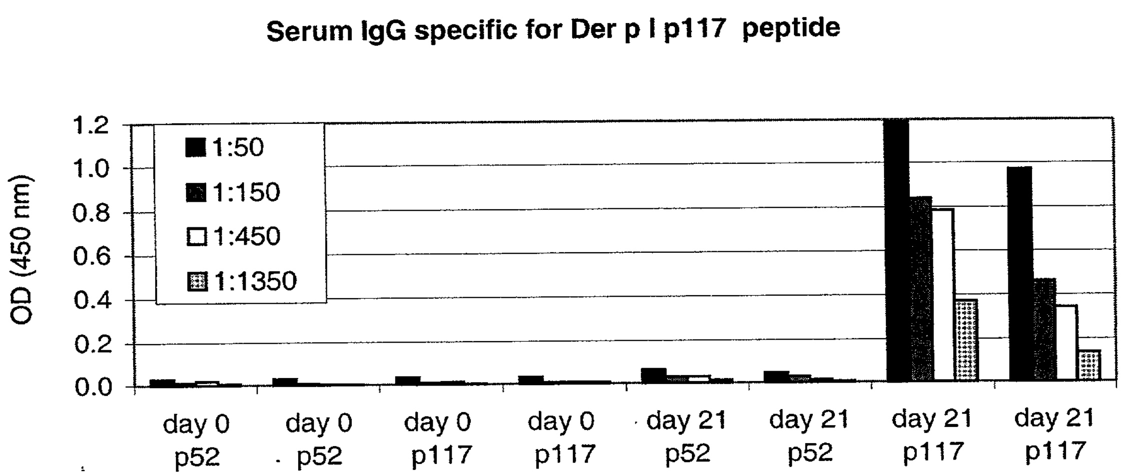

Serum IgG specific for Der p I p117 peptide
1.2
1.0
0.8
0.6
0.4
0.2
0.0
OD (450 nm)
1:50
1:150
1:450
1:1350
day 0 p52
day 0 p52
day 0 p117
day 0 p117
day 21 p52
day 21 p52
day 21 p117
day 21 p117

FIG. 10A

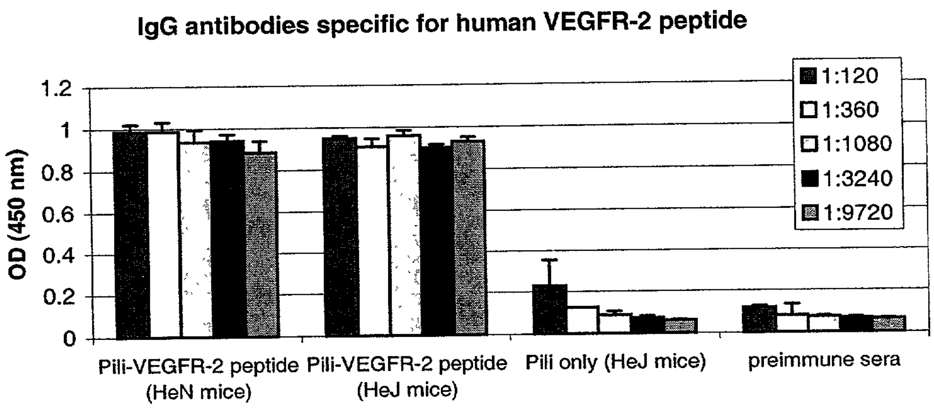


FIG. 10B

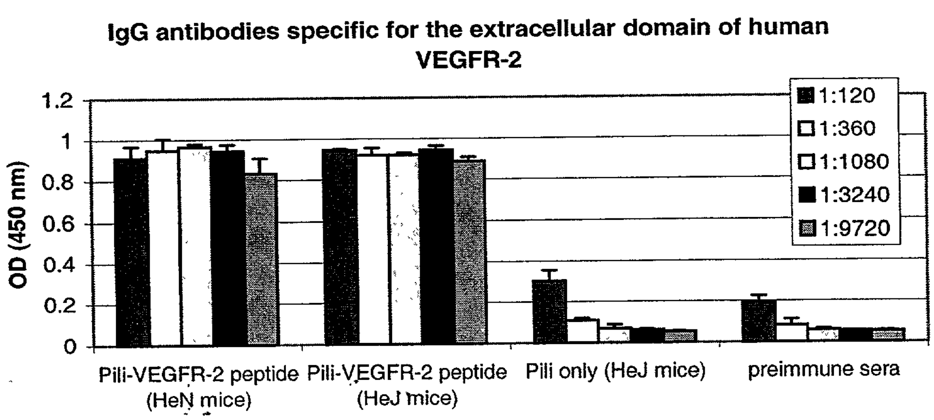


FIG. 11

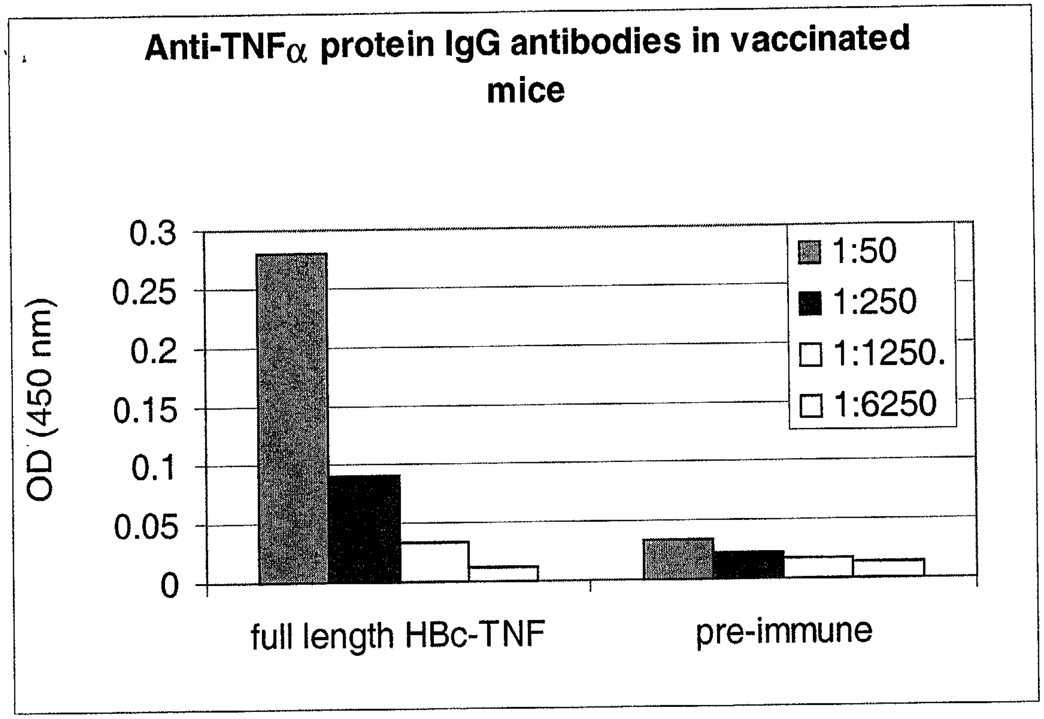
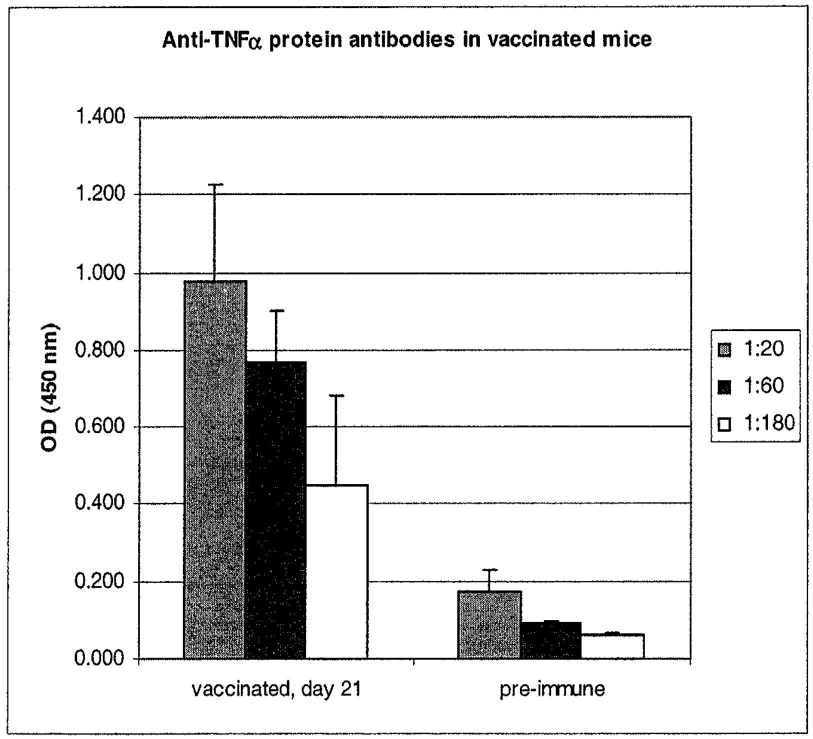

Anti-TNFα protein IgG antibodies in vaccinated mice
OD (450 nm)
0.3
0.25
0.2
0.15
0.1
0.05
0
1:50
1:250
1:1250.
1:6250
full length HBc-TNF
pre-immune

FIG. 12



Anti-TNFα protein antibodies in vaccinated mice
OD (450 nm)
1.400
1.200
1.000
0.800
0.600
0.400
0.200
0.000
vaccinated, day 21
pre-immune
1:20
1:60
1:180

FIG. 13A

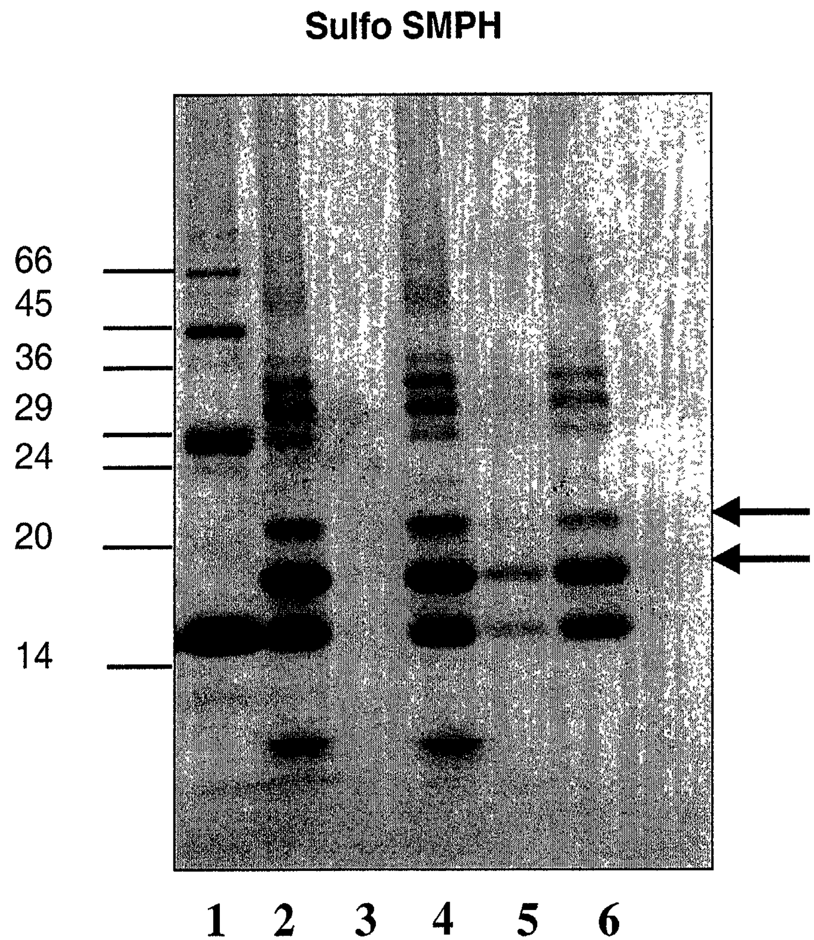


FIG. 13B

Sulfo SMPH

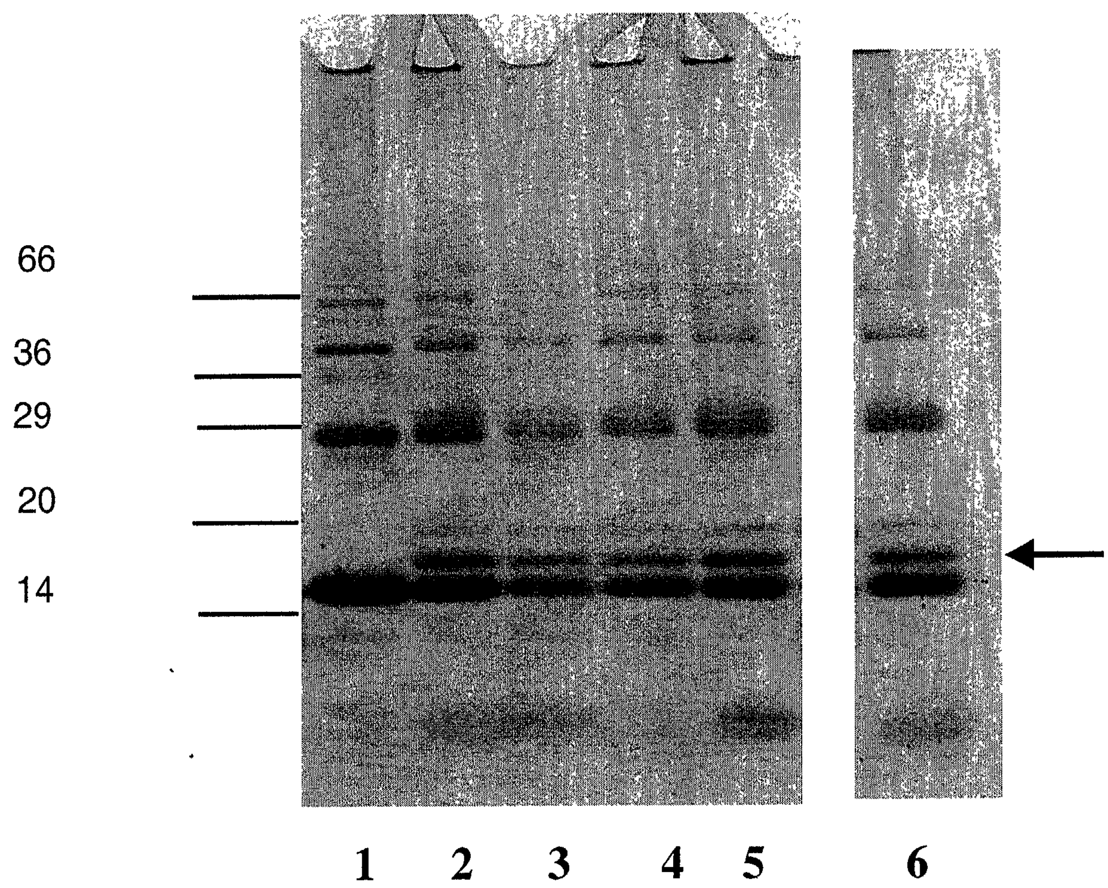


FIG. 13C

Sulfo SMPH

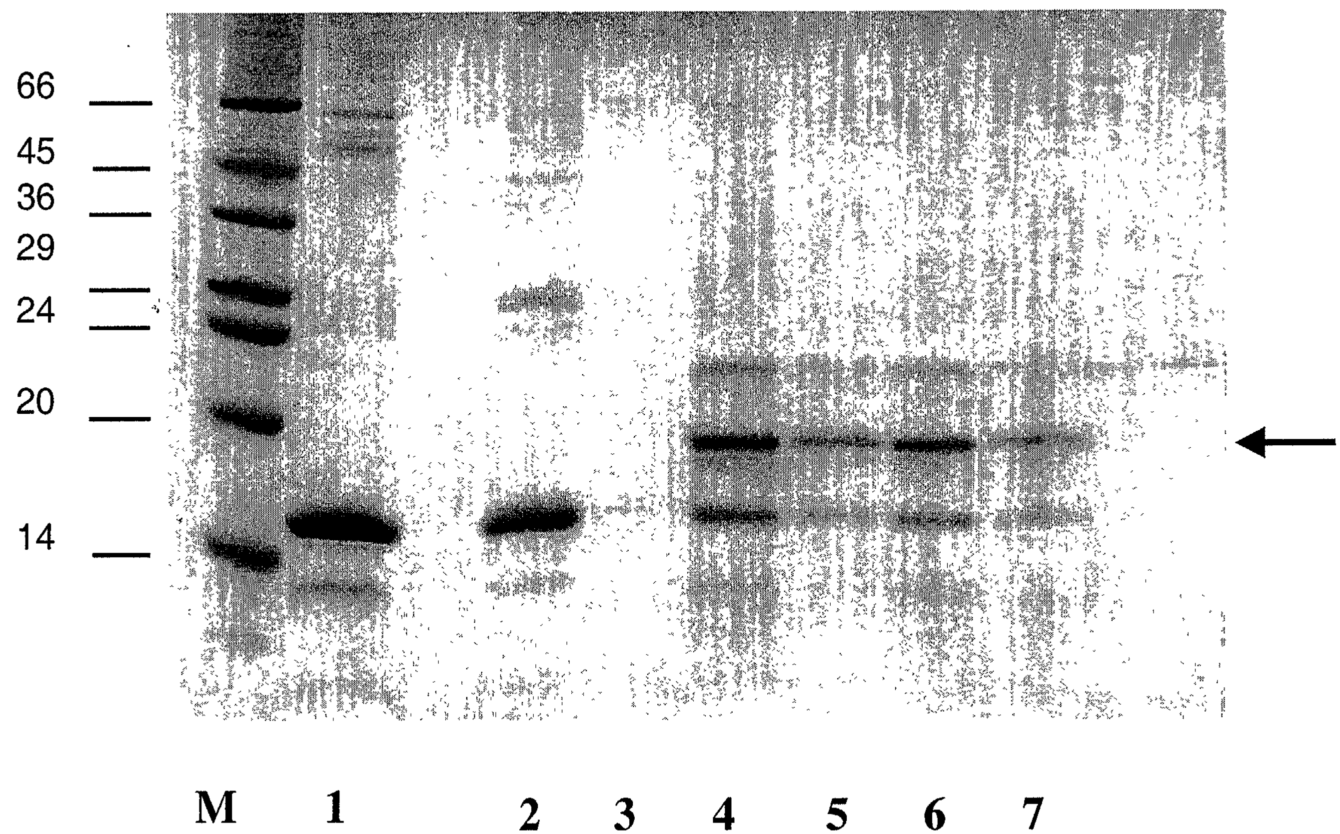


FIG. 13D

Sulfo GMBS

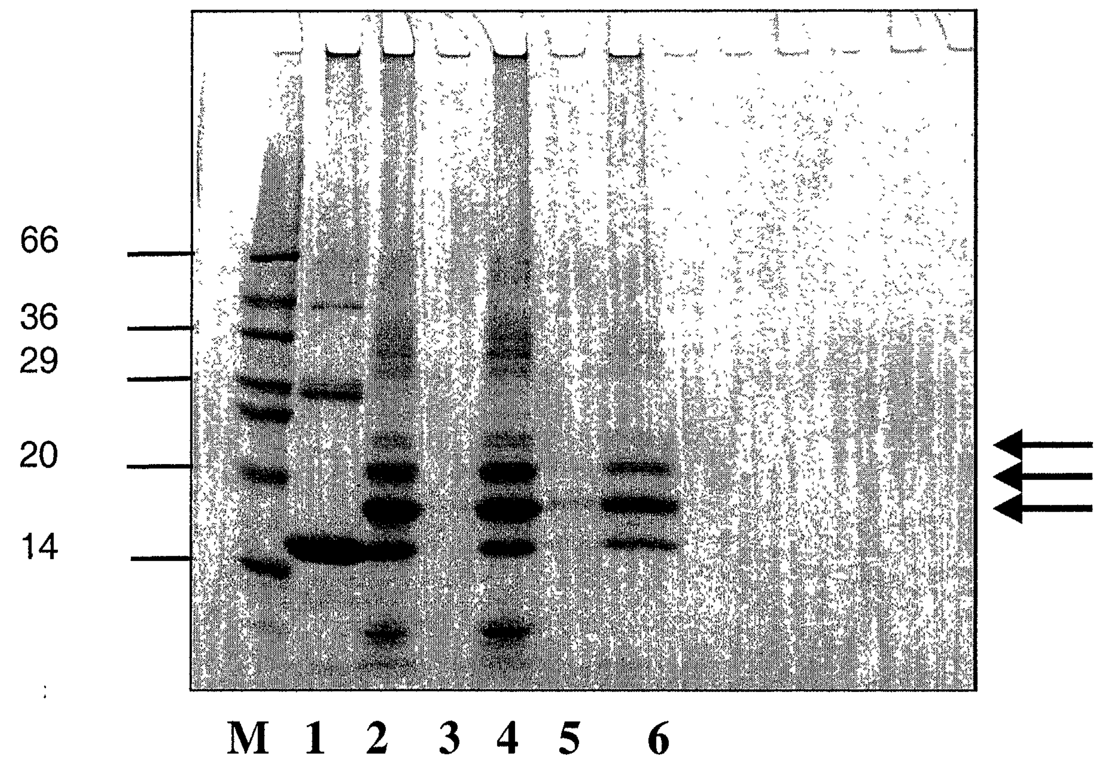


FIG. 13E

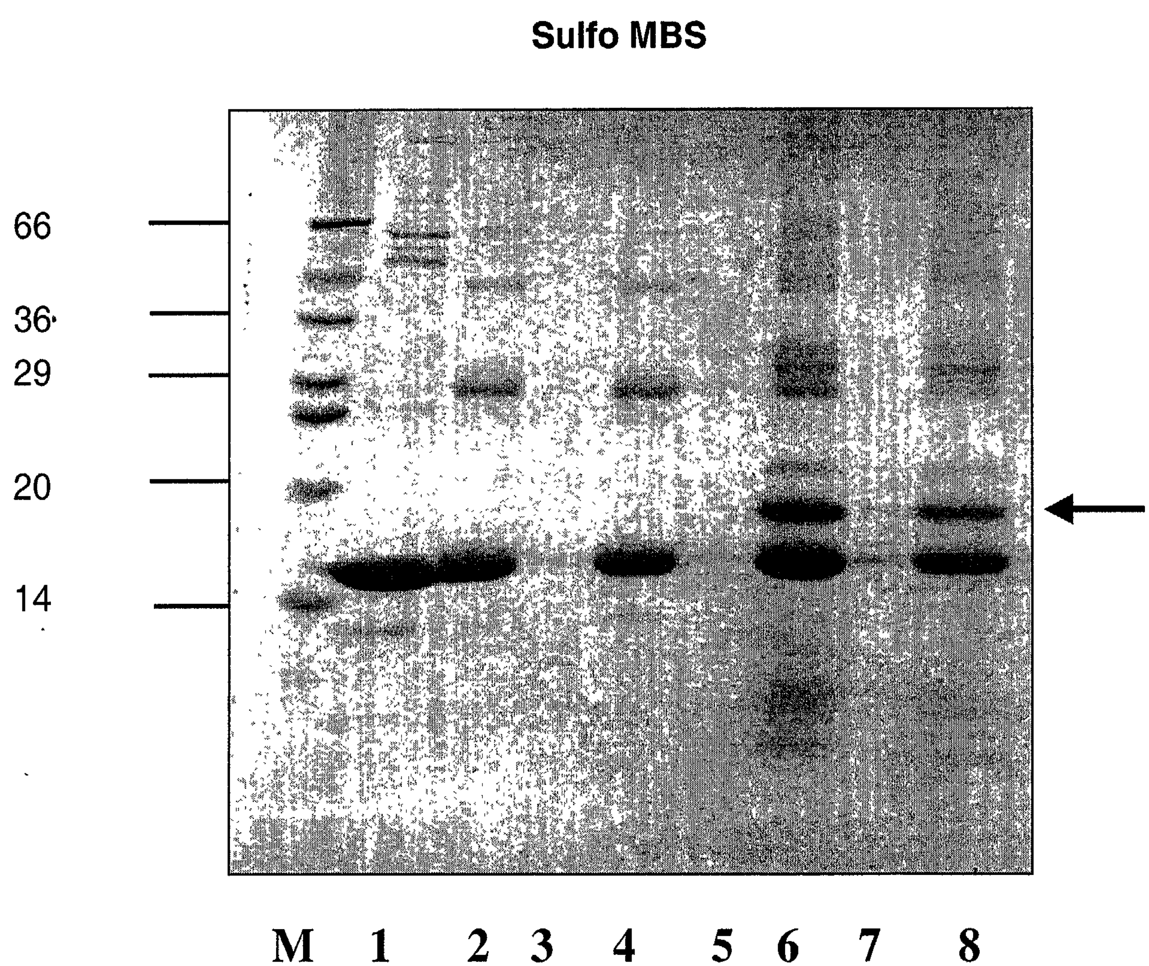


FIG. 14A

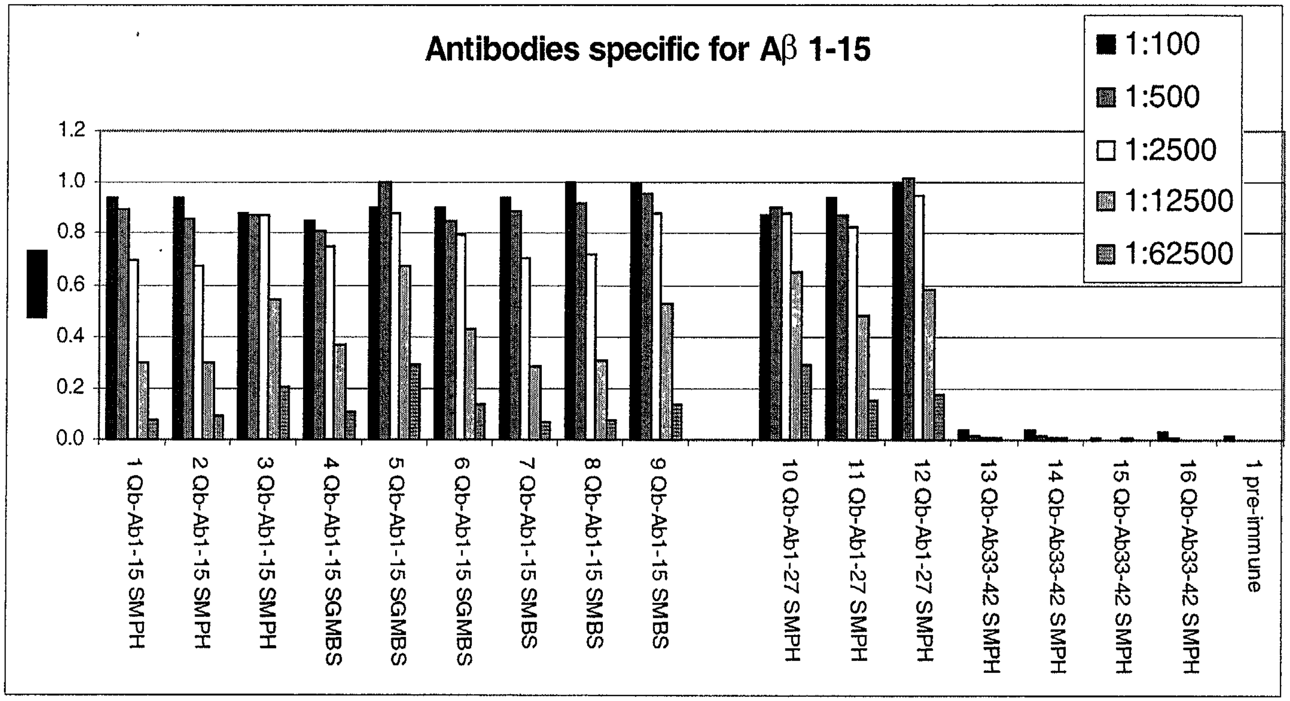

Antibodies specific for Aβ 1-15
1:100
1:500
1:2500
1:12500
1:62500
[redacted]
1.2
1.0
0.8
0.6
0.4
0.2
0.0
1 Qb-Ab1-15 SMPH
2 Qb-Ab1-15 SMPH
3 Qb-Ab1-15 SMPH
4 Qb-Ab1-15 SGMBS
5 Qb-Ab1-15 SGMBS
6 Qb-Ab1-15 SGMBS
7 Qb-Ab1-15 SMBS
8 Qb-Ab1-15 SMBS
9 Qb-Ab1-15 SMBS
10 Qb-Ab1-27 SMPH
11 Qb-Ab1-27 SMPH
12 Qb-Ab1-27 SMPH
13 Qb-Ab33-42 SMPH
14 Qb-Ab33-42 SMPH
15 Qb-Ab33-42 SMPH
16 Qb-Ab33-42 SMPH
1 pre-immune

FIG. 14B

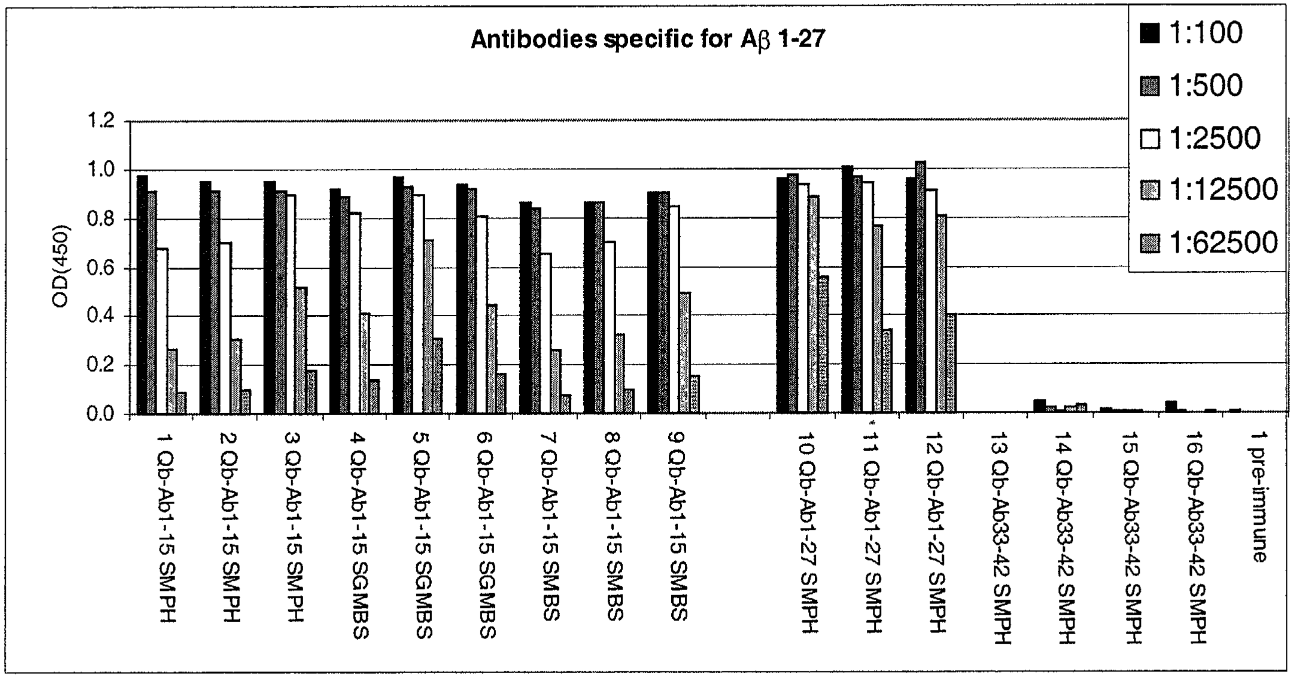
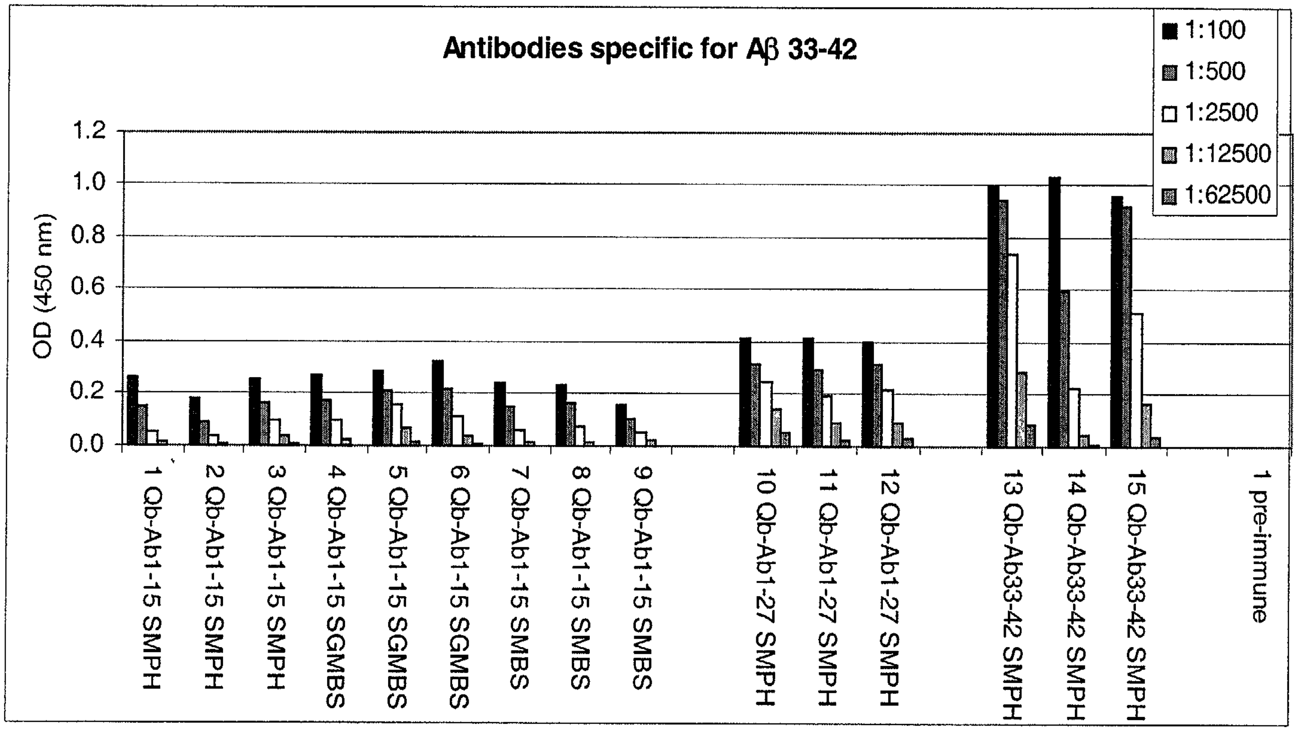
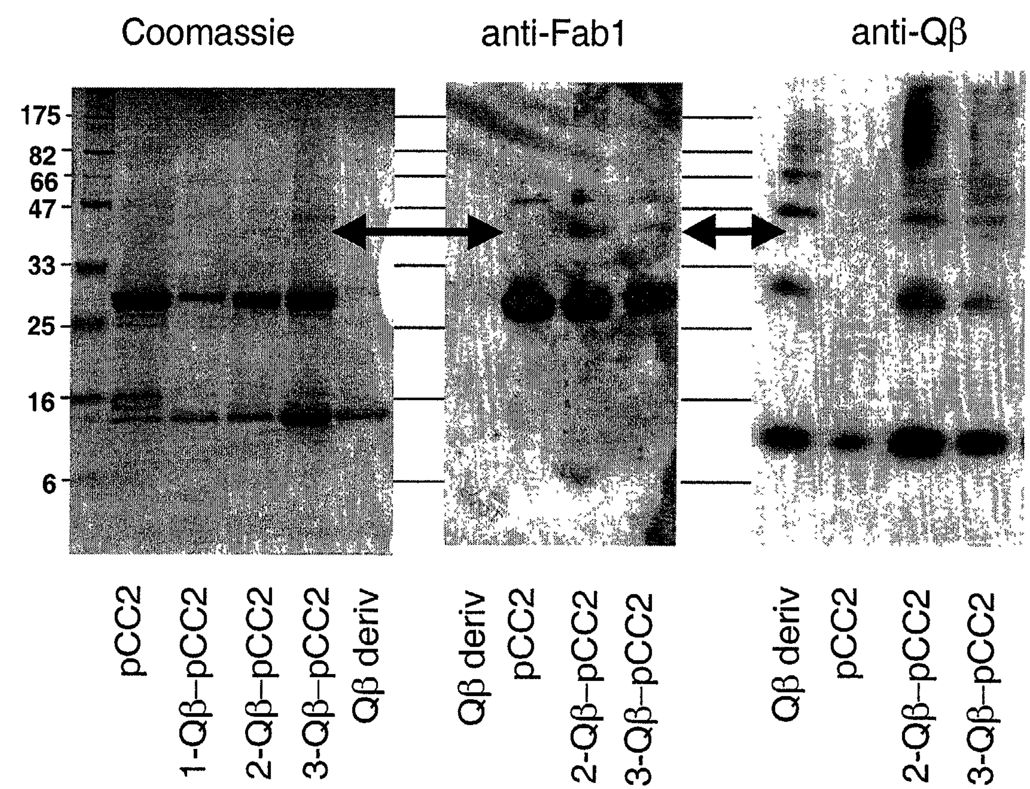

Antibodies specific for Aβ 1-27
1:100
1:500
1:2500
1:12500
1:62500
OD(450)
1.2
1.0
0.8
0.6
0.4
0.2
0.0
1 Qb-Ab1-15 SMPH
2 Qb-Ab1-15 SMPH
3 Qb-Ab1-15 SMPH
4 Qb-Ab1-15 SGMBS
5 Qb-Ab1-15 SGMBS
6 Qb-Ab1-15 SGMBS
7 Qb-Ab1-15 SMBS
8 Qb-Ab1-15 SMBS
9 Qb-Ab1-15 SMBS
10 Qb-Ab1-27 SMPH
11 Qb-Ab1-27 SMPH
12 Qb-Ab1-27 SMPH
13 Qb-Ab33-42 SMPH
14 Qb-Ab33-42 SMPH
15 Qb-Ab33-42 SMPH
16 Qb-Ab33-42 SMPH
1 pre-immune

FIG. 14C



Antibodies specific for Aβ 33-42
1:100
1:500
1:2500
1:12500
1:62500
OD (450 nm)
1.2
1.0
0.8
0.6
0.4
0.2
0.0
1 Qb-Ab1-15 SMPH
2 Qb-Ab1-15 SMPH
3 Qb-Ab1-15 SMPH
4 Qb-Ab1-15 SGMBS
5 Qb-Ab1-15 SGMBS
6 Qb-Ab1-15 SGMBS
7 Qb-Ab1-15 SMBS
8 Qb-Ab1-15 SMBS
9 Qb-Ab1-15 SMBS
10 Qb-Ab1-27 SMPH
11 Qb-Ab1-27 SMPH
12 Qb-Ab1-27 SMPH
13 Qb-Ab33-42 SMPH
14 Qb-Ab33-42 SMPH
15 Qb-Ab33-42 SMPH
1 pre-immune

FIG. 15A



Coomassie
anti-Fab1
anti-Qβ
175
82
66
47
33
25
16
6
pCC2
1-Qβ–pCC2
2-Qβ–pCC2
3-Qβ–pCC2
Qβ deriv
Qβ deriv
pCC2
2-Qβ–pCC2
3-Qβ–pCC2
Qβ deriv
pCC2
2-Qβ–pCC2
3-Qβ–pCC2

FIG. 15B

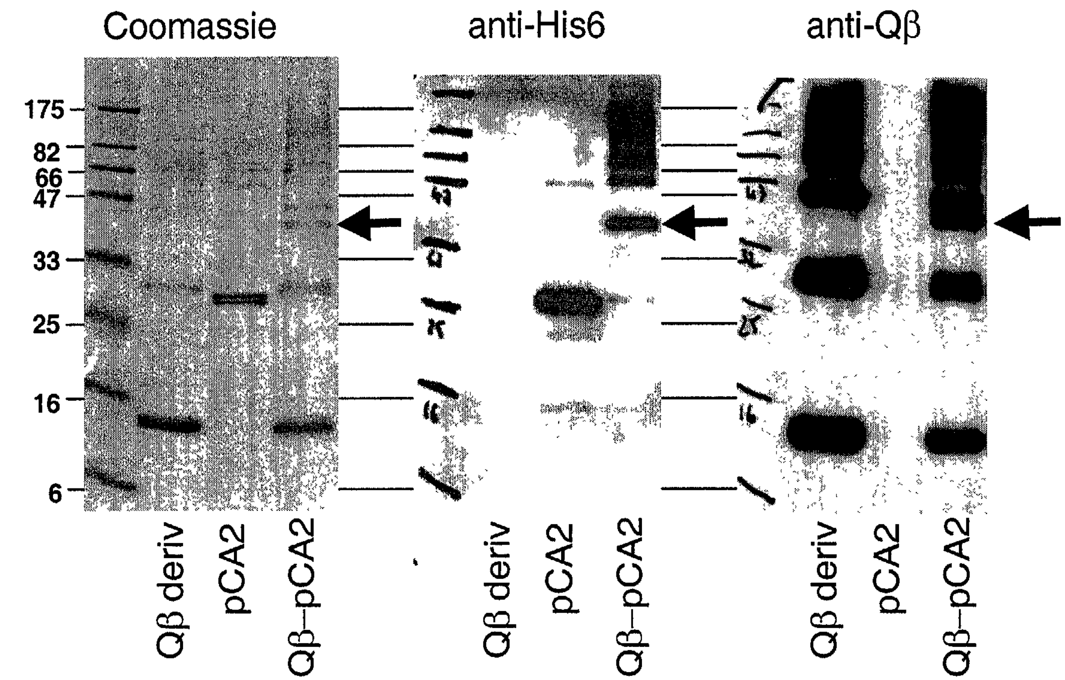
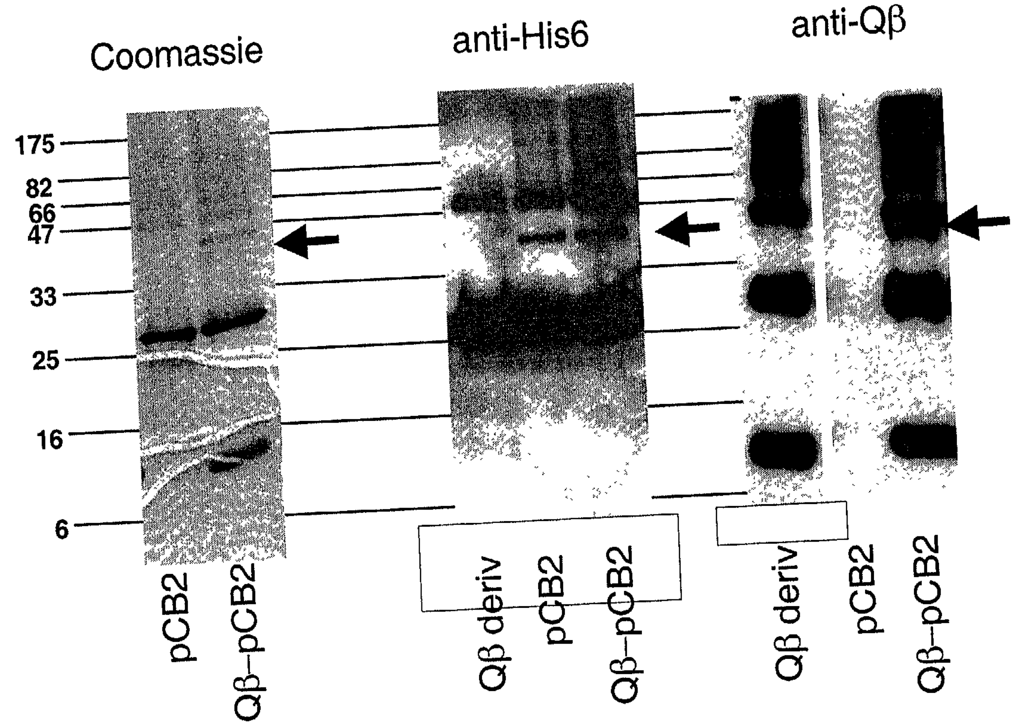

Coomassie
anti-His6
anti-Qβ
175
82
66
47
33
25
16
6
Qβ deriv
pCA2
Qβ–pCA2
Qβ deriv
pCA2
Qβ–pCA2
Qβ deriv
pCA2
Qβ–pCA2

FIG. 15C


Coomassie
anti-His6
anti-Qβ
175
82
66
47
33
25
16
6
pCB2
Qβ–pCB2
Qβ deriv
pCB2
Qβ–pCB2
Qβ deriv
pCB2
Qβ–pCB2

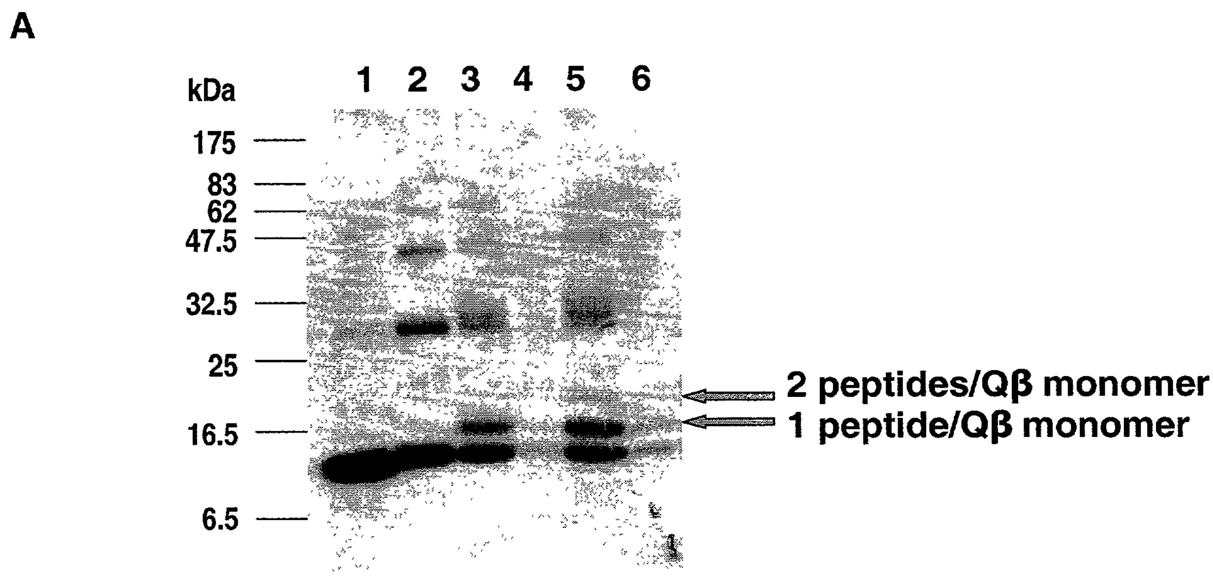


FIG. 16 A

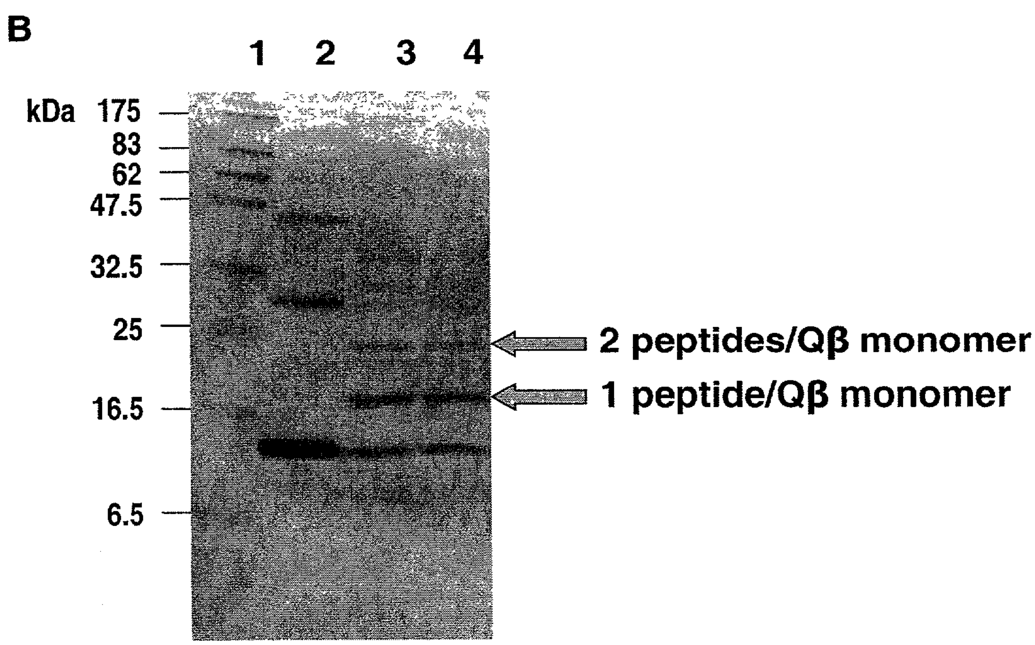


FIG. 16 B

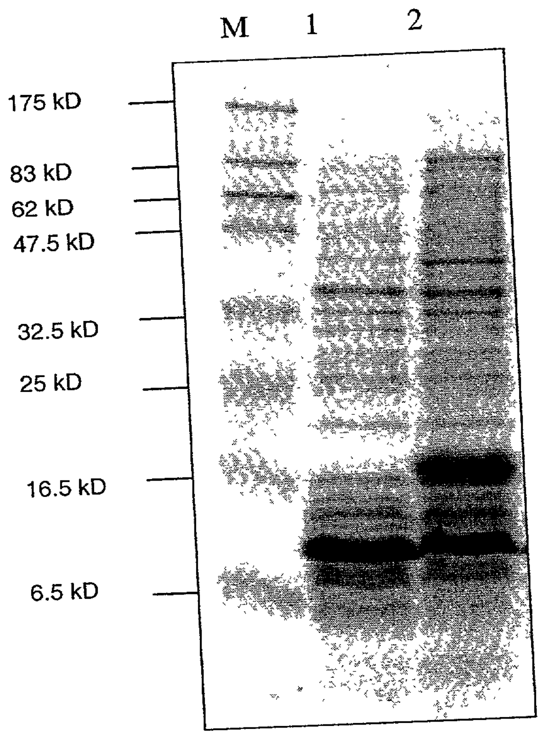


FIG. 17 A

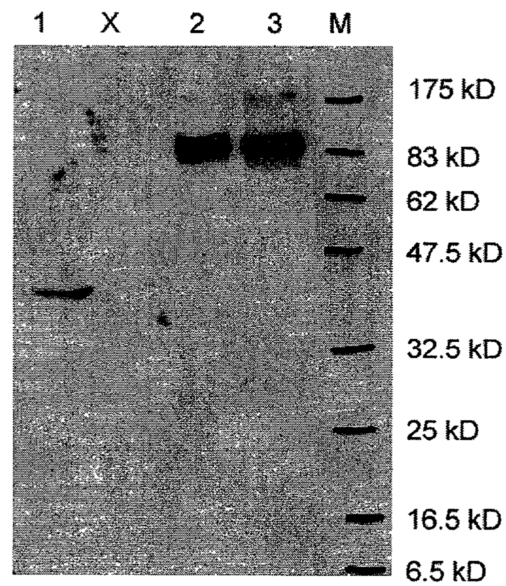


FIG. 17 B

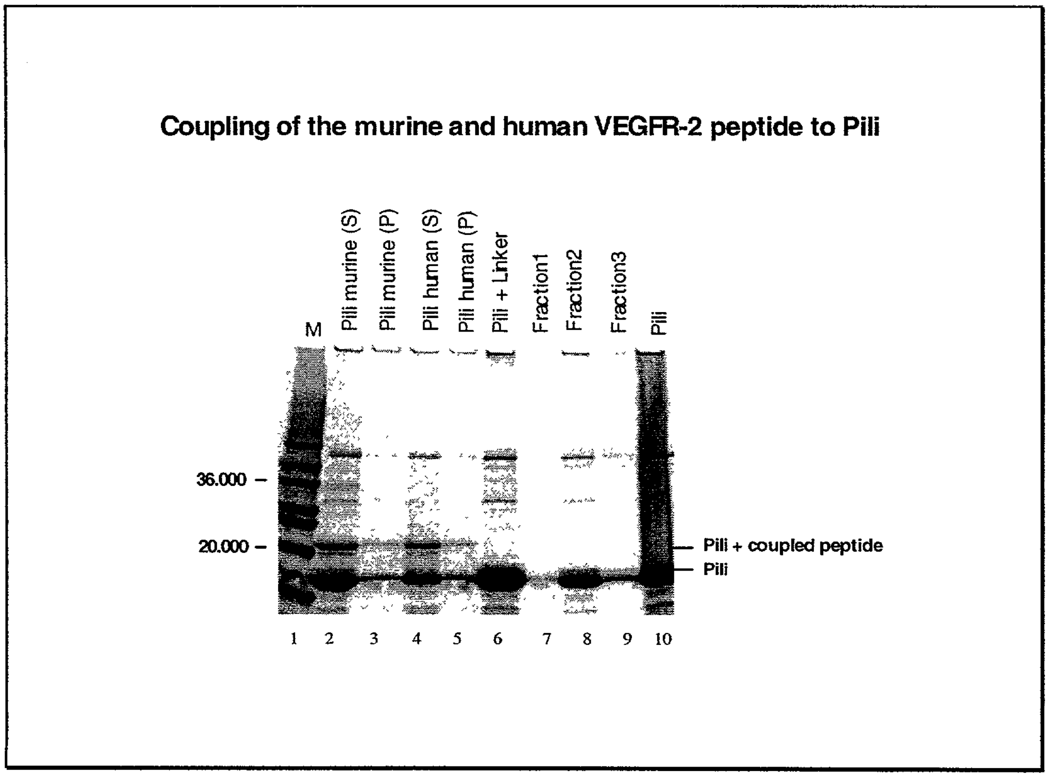

Coupling of the murine and human VEGFR-2 peptide to Pili
M
Pili murine (S)
Pili murine (P)
Pili human (S)
Pili human (P)
Pili + Linker
Fraction1
Fraction2
Fraction3
Pili
36.000 –
20.000 –
Pili + coupled peptide
Pili
1 2 3 4 5 6 7 8 9 10

FIG. 18 A

Coupling of the murine VEGFR-2 peptide to Qß

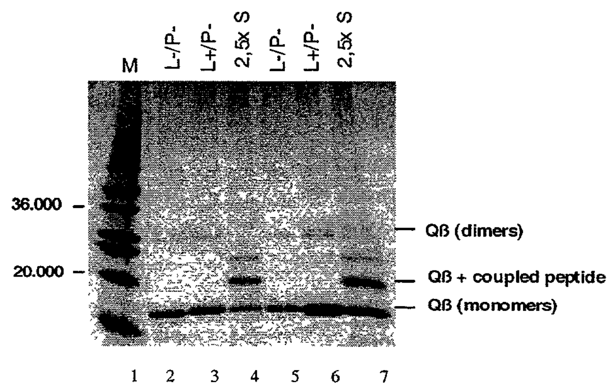


FIG. 18 B

Coupling of the murine VEGFR-2 peptide to cys-free HbcAg

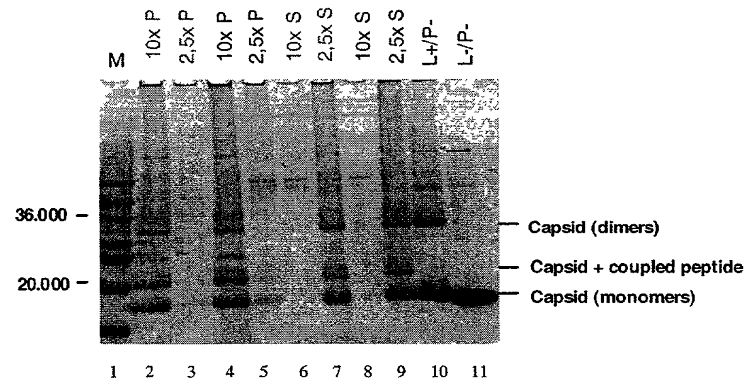


FIG. 18 C

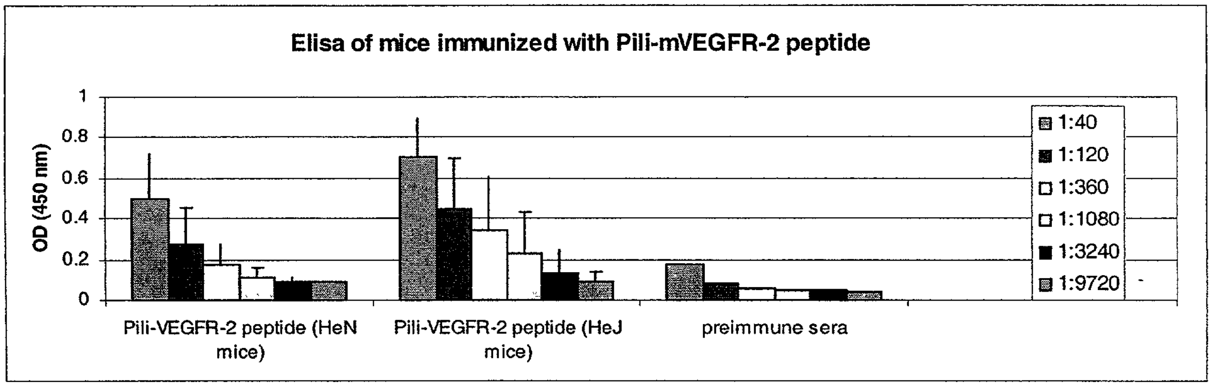

Elisa of mice immunized with Pili-mVEGFR-2 peptide
OD (450 nm)
1
0.8
0.6
0.4
0.2
0
1:40
1:120
1:360
1:1080
1:3240
1:9720
Pili-VEGFR-2 peptide (HeN mice)
Pili-VEGFR-2 peptide (HeJ mice)
preimmune sera

FIG. 18 D

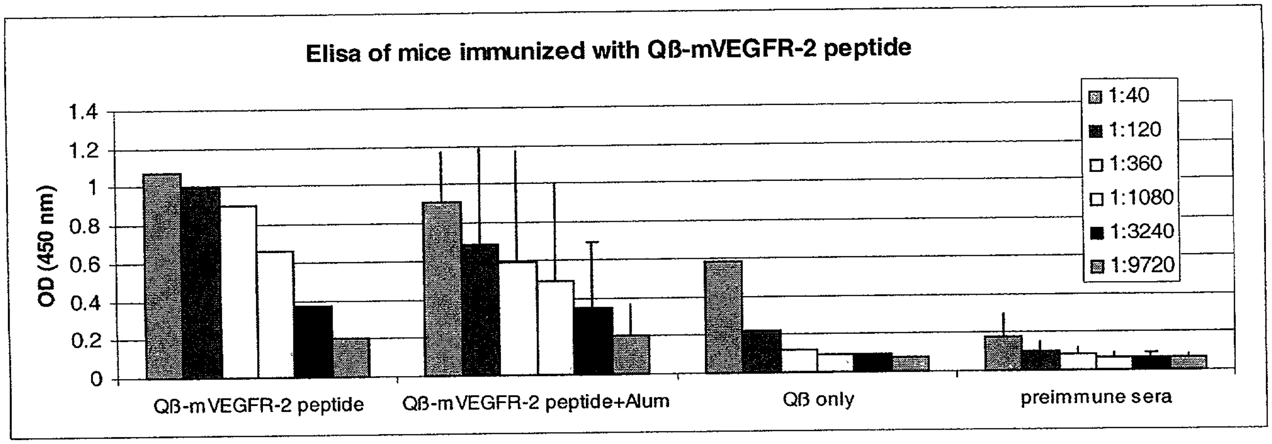

Elisa of mice immunized with QB-mVEGFR-2 peptide
1:40
1:120
1:360
1:1080
1:3240
1:9720
OD (450 nm)
1.4
1.2
1
0.8
0.6
0.4
0.2
0
QB-mVEGFR-2 peptide
QB-mVEGFR-2 peptide+Alum
QB only
preimmune sera

FIG. 18 E

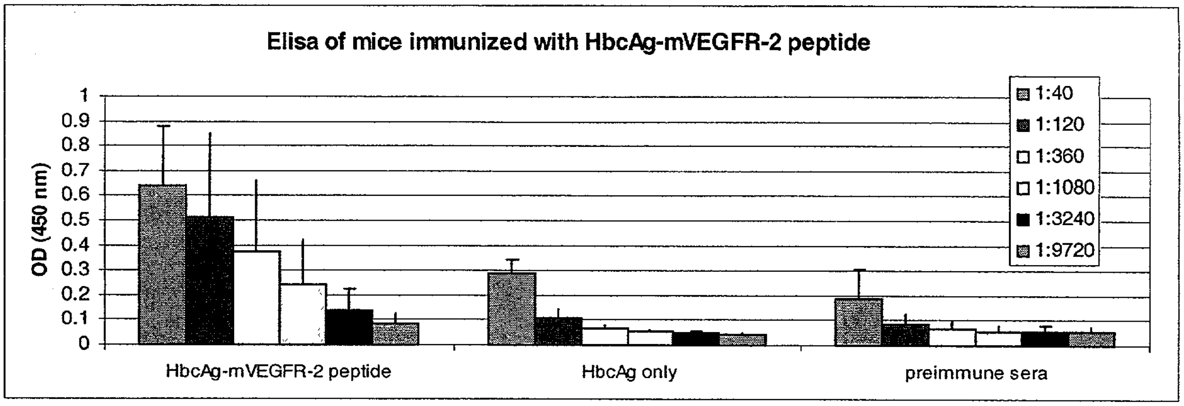

Elisa of mice immunized with HbcAg-mVEGFR-2 peptide
OD (450 nm)
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1:40
1:120
1:360
1:1080
1:3240
1:9720
HbcAg-mVEGFR-2 peptide
HbcAg only
preimmune sera

FIG. 18 F

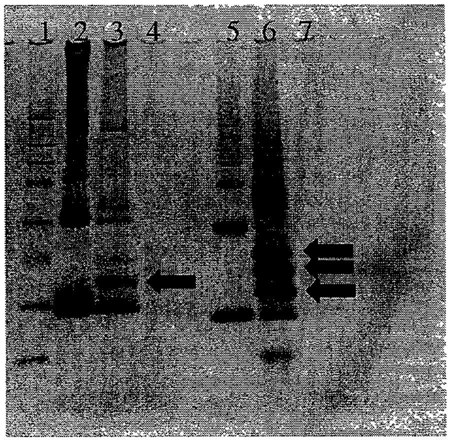


FIG. 19 A

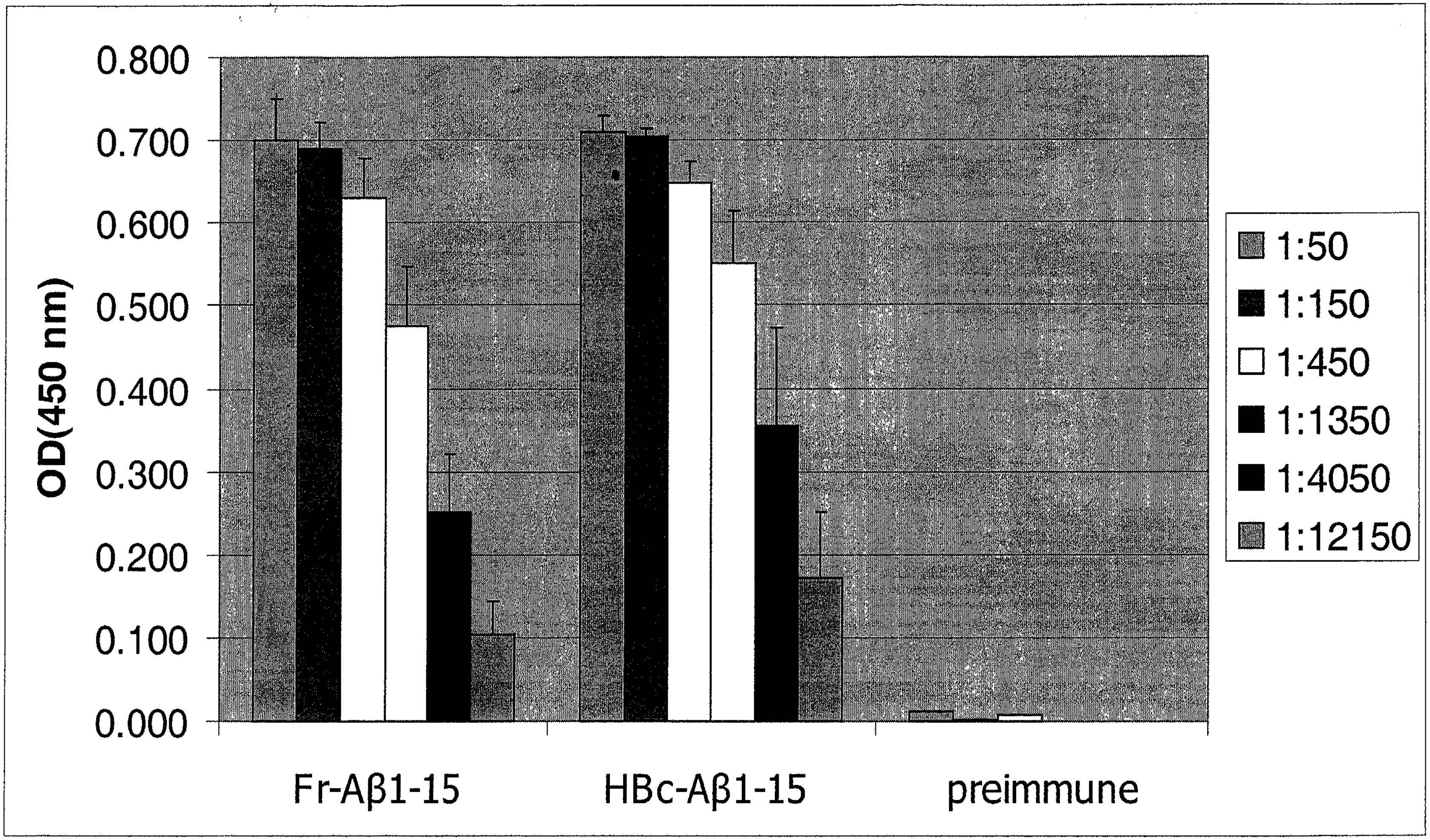

0.800
0.700
0.600
0.500
0.400
0.300
0.200
0.100
0.000
OD(450 nm)
Fr-Aβ1-15
HBc-Aβ1-15
preimmune
1:50
1:150
1:450
1:1350
1:4050
1:12150

FIG. 19 B

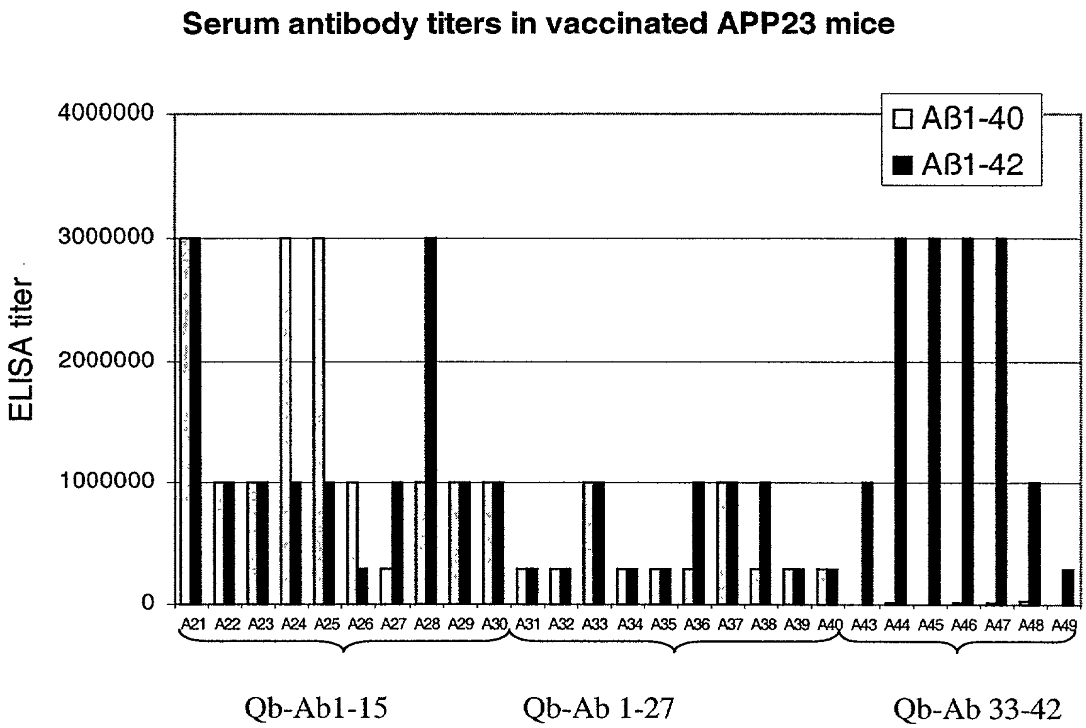

Serum antibody titers in vaccinated APP23 mice
ELISA titer
4000000
3000000
2000000
1000000
0
□ Aß1-40
■ Aß1-42
A21 A22 A23 A24 A25 A26 A27 A28 A29 A30 A31 A32 A33 A34 A35 A36 A37 A38 A39 A40 A43 A44 A45 A46 A47 A48 A49
Qb-Ab1-15
Qb-Ab 1-27
Qb-Ab 33-42

FIG. 20

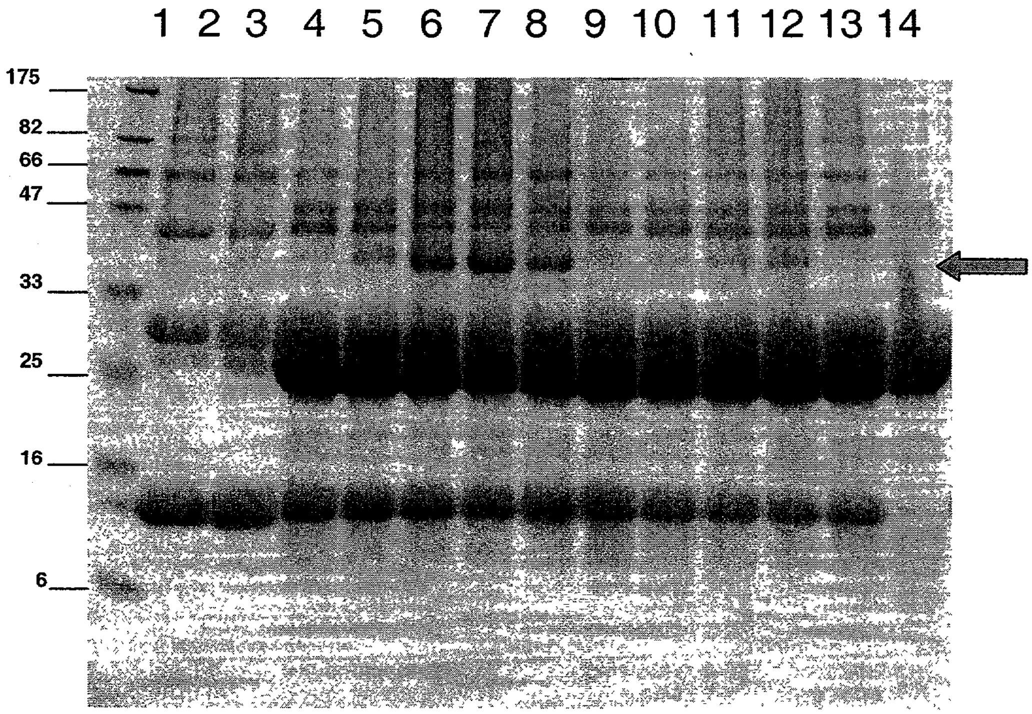


FIG. 21

Fig Qb mut S-MBS Flag

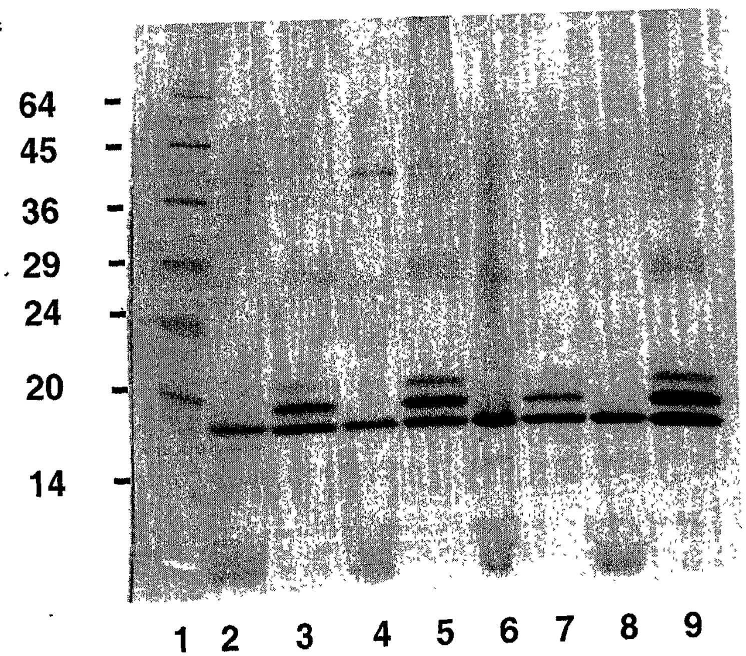


FIG. 22 A

Fig Qb mut SGMBS Flag

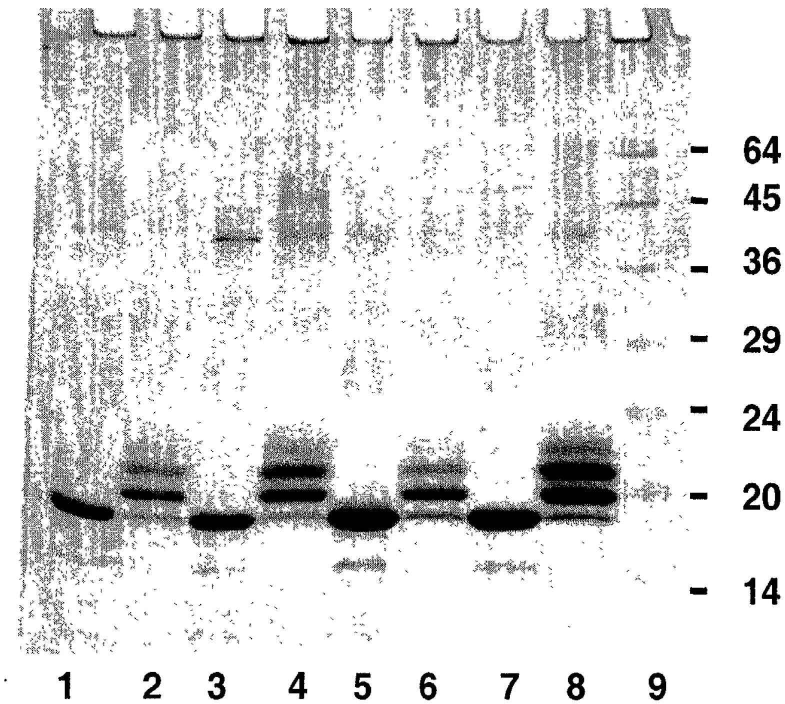


FIG. 22 B

Fig Qb mut SMPH Flag

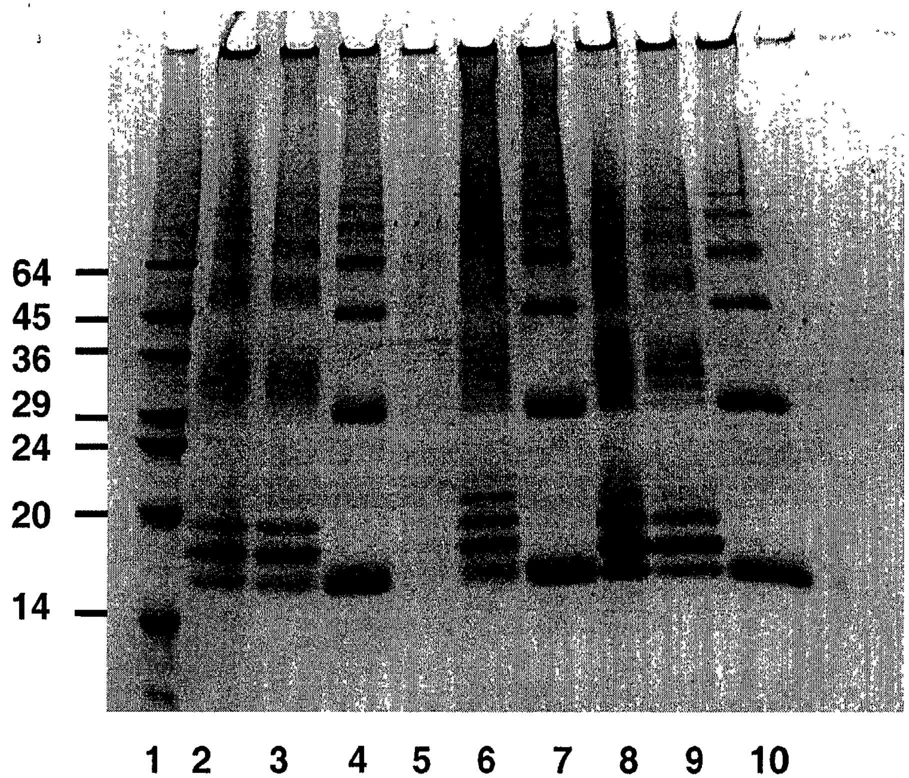


FIG. 22 C

Fig Qβ mutants-PLA_2-Cys

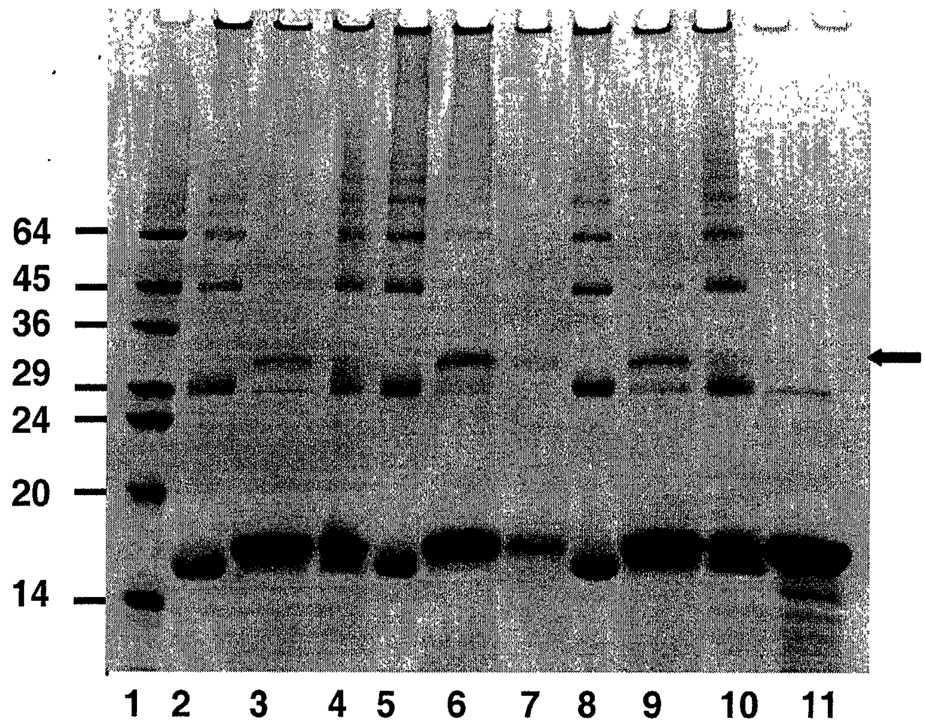


FIG. 22 D

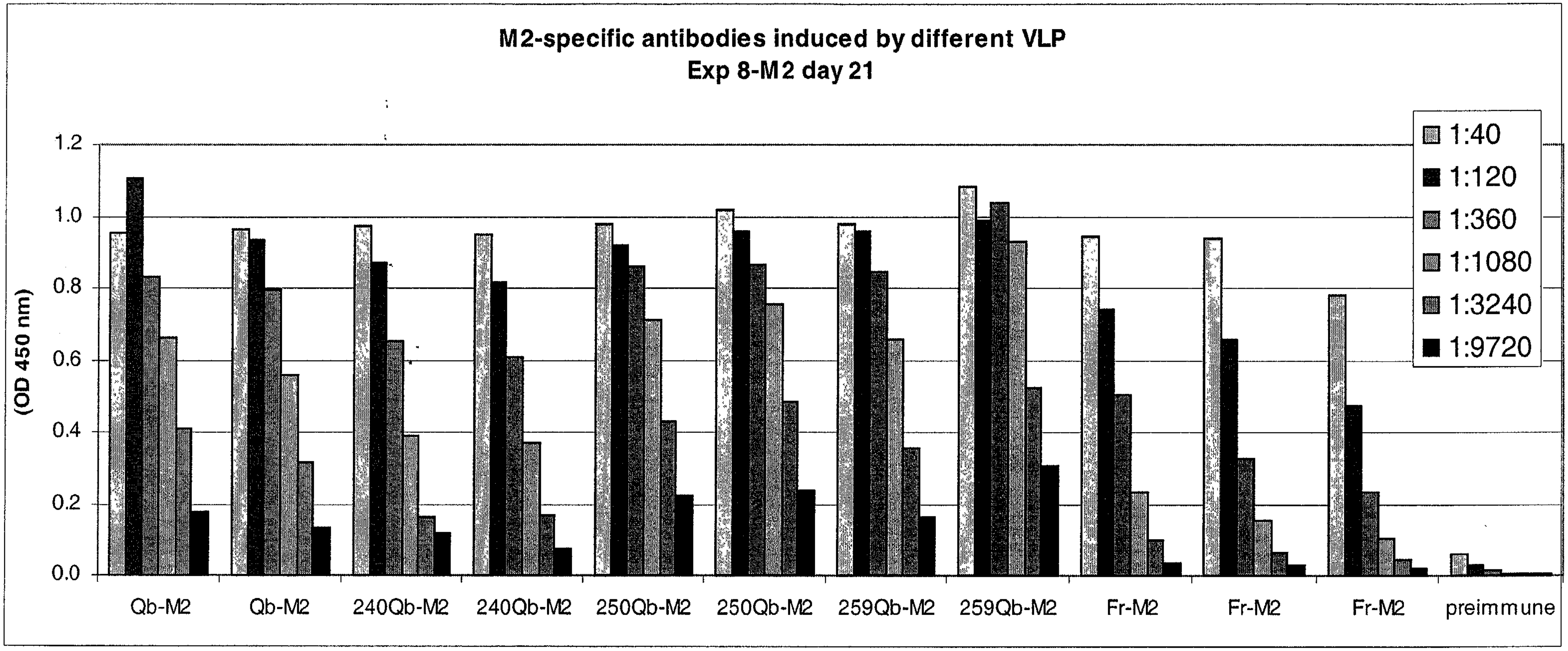

M2-specific antibodies induced by different VLP
Exp 8-M2 day 21
(OD 450 nm)
1.2
1.0
0.8
0.6
0.4
0.2
0.0
1:40
1:120
1:360
1:1080
1:3240
1:9720
Qb-M2
Qb-M2
240Qb-M2
240Qb-M2
250Qb-M2
250Qb-M2
259Qb-M2
259Qb-M2
Fr-M2
Fr-M2
Fr-M2
preimmune

FIG. 23

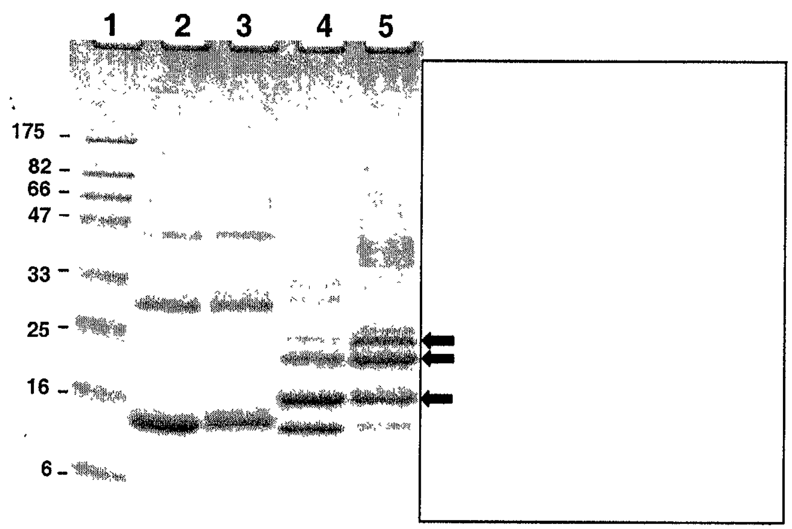


FIG. 24

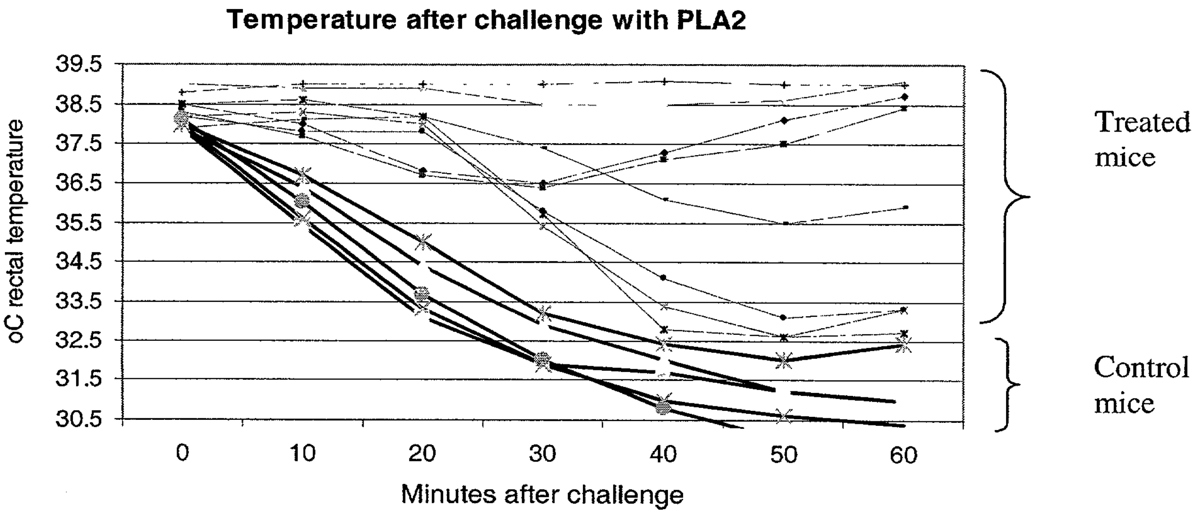

Temperature after challenge with PLA2
39.5
38.5
37.5
36.5
35.5
34.5
33.5
32.5
31.5
30.5
oC rectal temperature
0
10
20
30
40
50
60
Minutes after challenge
Treated mice
Control mice

FIG. 25 A

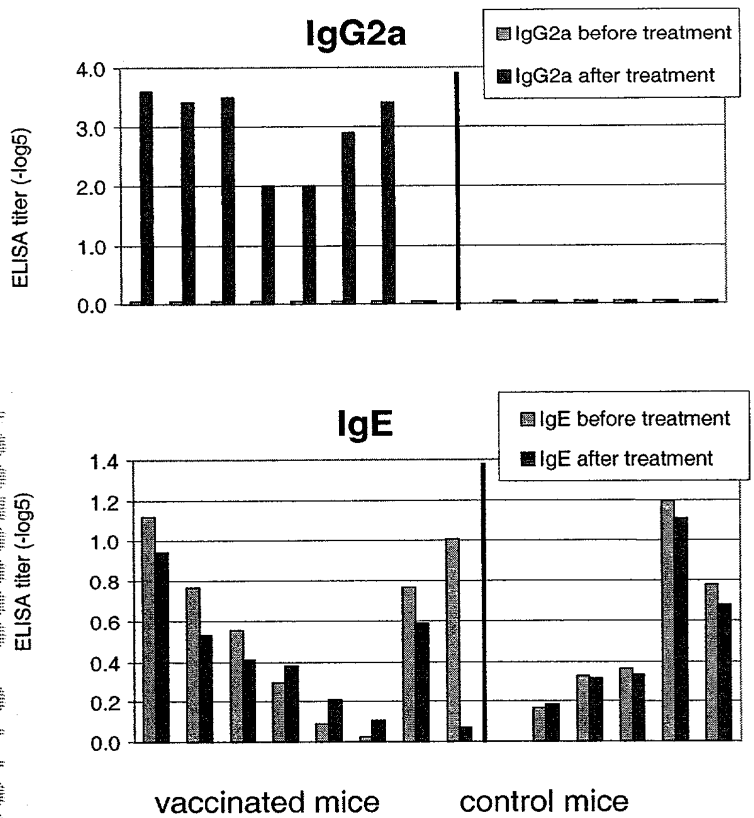

IgG2a
IgG2a before treatment
IgG2a after treatment
4.0
3.0
2.0
1.0
0.0
ELISA titer (-log5)
IgE
IgE before treatment
IgE after treatment
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
ELISA titer (-log5)
vaccinated mice
control mice

FIG. 25 B

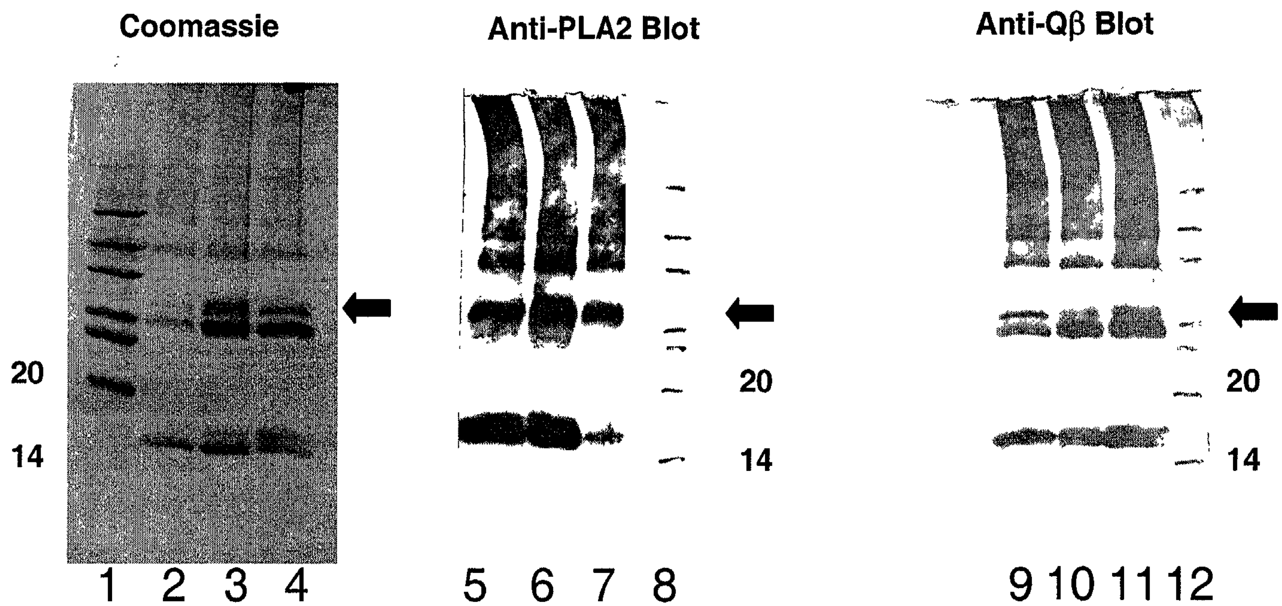

Coomassie
Anti-PLA2 Blot
Anti-Qβ Blot
20
14
20
14
20
14
1 2 3 4
5 6 7 8
9 10 11 12

FIG. 26

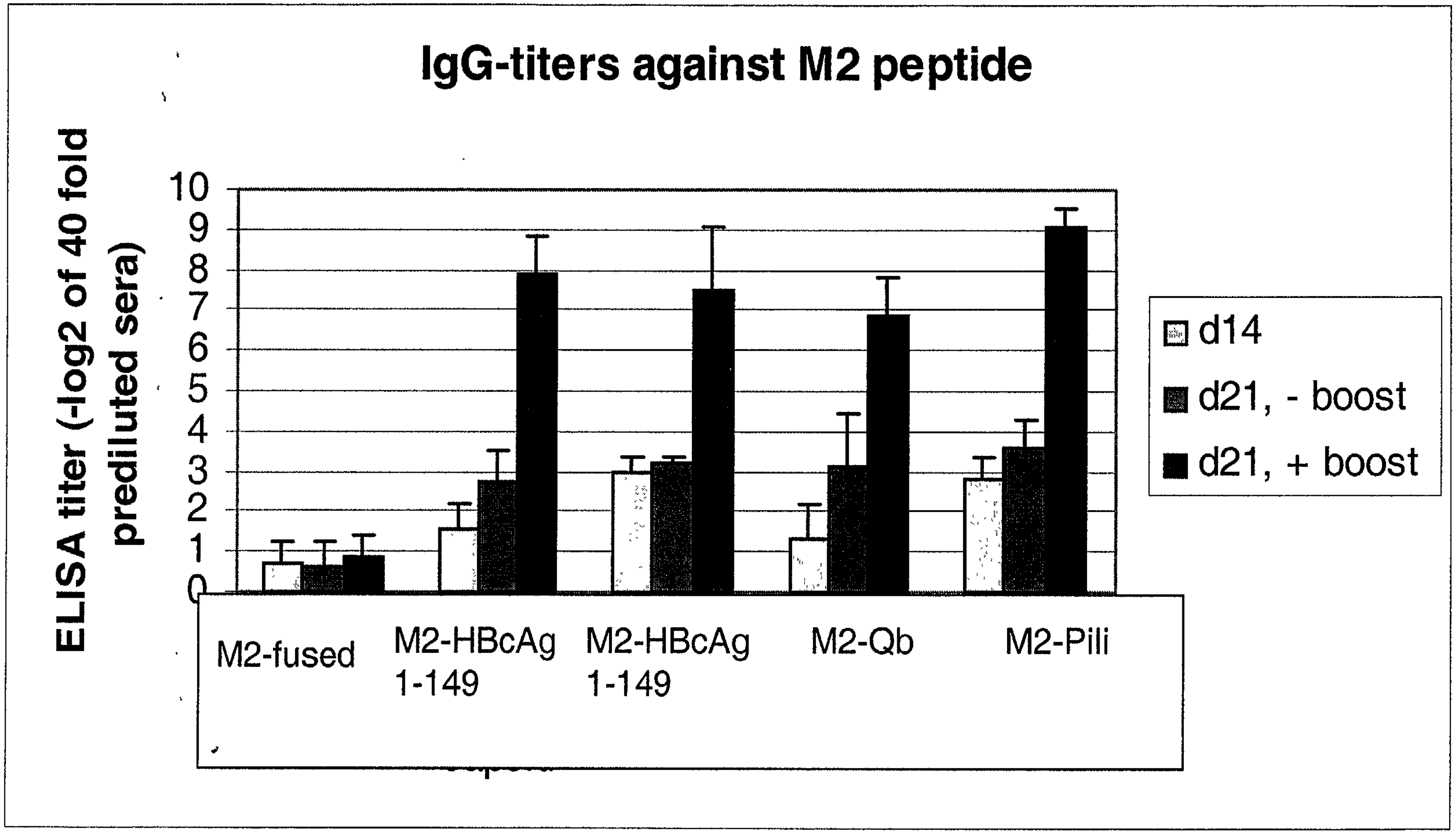
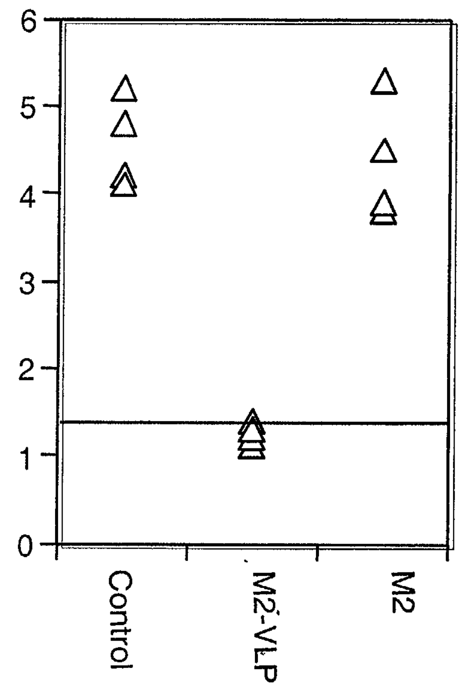

IgG-titers against M2 peptide
ELISA titer (-log2 of 40 fold prediluted sera)
0
1
2
3
4
5
6
7
8
9
10
M2-fused
M2-HBcAg 1-149
M2-HBcAg 1-149
M2-Qb
M2-Pili
d14
d21, - boost
d21, + boost

FIG. 27 A



Survival of mice vaccinated intravenesly followed by a lethal influenza A challenge

Immunization	Survival
M2 coupled to VLP	6/6
M2 fused to VLP	0/3
Control	0/6

FIG. 27 B

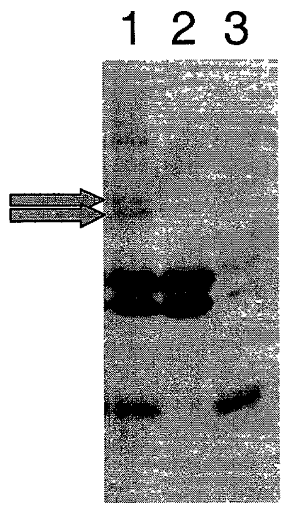
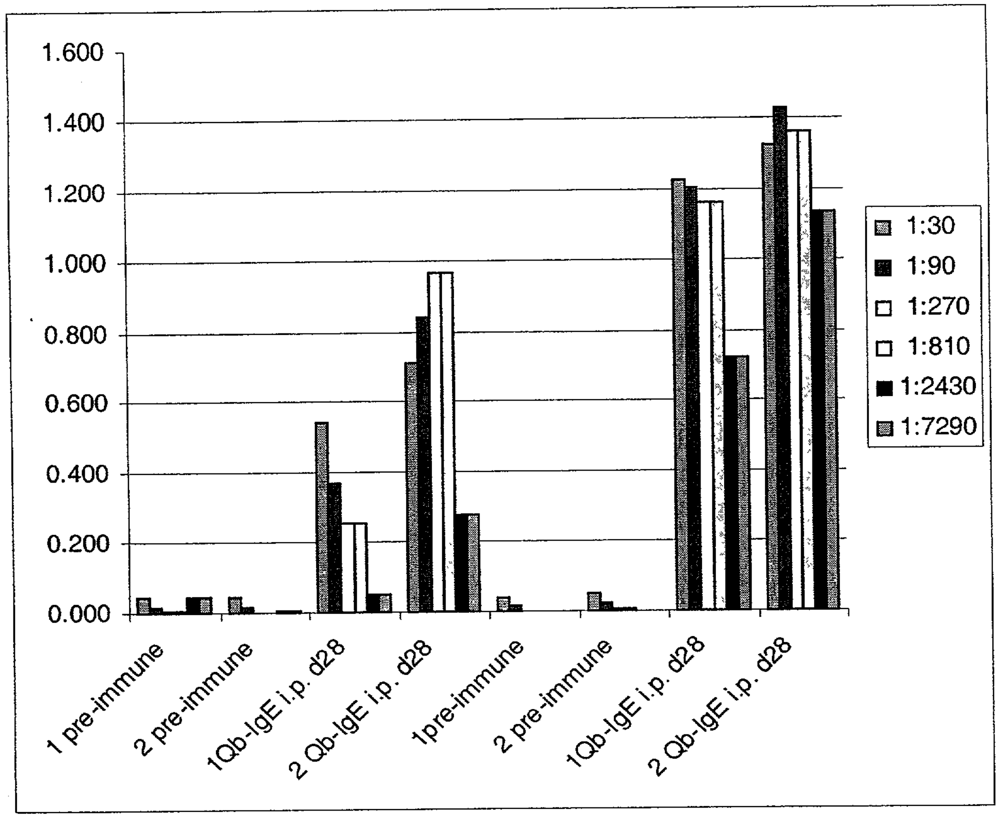


FIG. 28 A



1.600
1.400
1.200
1.000
0.800
0.600
0.400
0.200
0.000
1:30
1:90
1:270
1:810
1:2430
1:7290
1 pre-immune
2 pre-immune
1Qb-IgE i.p. d28
2 Qb-IgE i.p. d28
1pre-immune
2 pre-immune
1Qb-IgE i.p. d28
2 Qb-IgE i.p. d28

FIG. 28 B